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Updated Mutagenicity and Carcinogenicity Assessment of Cadmium: Addendum to the Health Assessment Document for Cadmium

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This document concludes that: (1) there is mixed evidence on the mutagenicity of various cadmium salts; (2) cadmium chloride aerosol induces lung cancer in rats; (3) injected cadmium salts induce injection site sarcomas and testicular tumors in both mice and rats; (4) there is limited epidemiologic evidence that inhaled cadmium is dose-related to lung cancer in exposed workers; (5) there is no evidence that cadmium is carcinogenic via ingestion, which is a major route of human exposure, and the upper limit of potency via ingestion is at least 100 times less than via inhalation.

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ABSTRACT

This document evaluates the mutagenicity and carcinogenicity of cadmium, supplementing an earlier document (Health Assessment Document for Cadmium, May 1981) which dealt with all health effects. Since the earlier document was prepared, a rat inhalation carcinogenicity study has been reported and several epidemiology and mutagenicity papers have been published.

This document concludes that: (1) there is mixed evidence on the mutagenicity of various cadmium salts; (2) cadmium chloride aerosol induces lung cancer in rats; (3) injected cadmium salts induce injection site sarcomas and testicular tumors in both mice and rats; (4) there is limited epidemiologic evidence that inhaled cadmium is dose-related to lung cancer in exposed workers; (5) there is no evidence that cadmium is carcinogenic via ingestion, which is a major route of human exposure, and the upper limit of potency via ingestion is at least 100 times less than via inhalation.

PREFACE

This document, a review and assessment of the current information relating to the mutagenicity and carcinogenicity of cadmium, contains a detailed discussion of information on those subjects that became available since the earlier Health Assessment Document for Cadmium was prepared by the Office of Health and Environmental Assessment (OHEA) in May 1981. The literature search supporting the carcinogenicity assessment is current through November 1984, although an updated Thun et al. (1985) study is included; the literature search supporting the mutagenicity section is current through December 1983.

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SUMMARY AND CONCLUSIONS

SUMMARY

Qualitative Assessment

Cadmium has been investigated for mutagenic activity in both prokaryotic and eukaryotic systems. Gene mutation studies in *Salmonella typhimurium* and *E. coli* have produced inconclusive results. In yeast, gene mutation studies have also been inconclusive. In three gene mutation studies (in mammalian cell cultures, mouse lymphoma cells, and Chinese hamster lung and ovary cells) marginally positive responses to cadmium were observed.

Rec-assay in *Bacillus subtilis* resulted in a weak mutagenic response. In the Drosophila sex-linked recessive lethal test, cadmium was found to be nonmutagenic. The dominant lethal test in Drosophila resulted in a positive response with a dose-response relationship.

The results of chromosomal aberration studies in human lymphocytes from exposed workers and human cell lines treated with cadmium have been conflicting. In Chinese hamster cells, chromosomal aberrations were noted following treatment with cadmium; however, in mouse carcinoma cells, no aberrations were recorded in response to cadmium treatment. In rodents, treatment with cadmium did not induce chromosomal aberrations or micronuclei in bone marrow cells. Similarly, no dominant lethal mutations or heritable translocations were noted in mice treated with cadmium.

The evidence that cadmium interferes with spindle formation comes from both *in vitro* and *in vivo* studies in mammals. In *in vitro* studies using the Chinese hamster cell line "Hy," cadmium induced an effect similar to that of colchicine, which is a known spindle poison. Cadmium also was found to increase numerical chromosome aberrations (aneuploidy) in these cells. Similar results were obtained in studies on aneuploidy in whole mammals. In female mice and Syrian hamsters, cadmium induced chromosomal nondisjunction leading to aneuploidy in germ cells. A recent study demonstrated that the numerical aberrations induced by cadmium chloride in female germ cells of mice are inherited in the embryos.

Chronic exposure of rats to aerosols of cadmium chloride at airborne concentrations of 12.5, 25, and 50 $\mu g/m^3$ cadmium as cadmium chloride for 18 months followed by a nonexposed 13-month period produced significant increases in lung tumors (Takenaka et al., 1983). A single 30-minute exposure of rats to cadmium oxide at a concentration of 60 mg/m^3 did not significantly increase the occurrence of lung tumors in the year that followed, although increases in testicular degeneration were observed. The estimated total dose in mg/kg was, however, lower than that producing testicular neoplasia following parenteral administration (Poirier et al., 1983). Intratracheal instillation of cadmium oxide produced an increase in mammary tumors and an increase in tumors at multiple sites among male rats (Sanders and Mahaffey, 1984). Intrathoracic injections of cadmium powder were found to be highly toxic, but when their toxicity was reduced by co-administration of zinc, mesotheliomas developed (Furst et al., 1973). Intramuscular or subcutaneous injection of cadmium as metal powder, or as the chloride, sulfate, oxide, or sulfide, produced injection-site sarcomas and/or testicular interstitial cell (Leydig cell) tumors in rats after necrosis and regeneration of testicular tissue (Table 10). One study suggested that the incidence of pancreatic islet cell tumors in laboratory animals may be increased by administering cadmium chloride by injection (Poirier et al., 1983). In another study, injection of cadmium chloride into the prostate gland induced tumors of that tissue in male rats (Scott and Aughey, 1979).

Cadmium appears to be much less potent a carcinogen by ingestion than by injection or inhalation. For example, the total dose of inhaled cadmium in the Takenaka et al. (1983) study, in which rats developed a 71% incidence of lung cancer, was about 7 mg (0.25 m^3/day x 0.005 mg/m^3 x 365 days/year x 1.5 years). The potency value derived from this study is 0.7/7 (0.1). By contrast, the greatest reasonable potency for cadmium by ingestion was estimated to be 0.0017, or only about 1/100 that by inhalation. Since all ingestion studies were negative for cancer induction, the Schroeder et al. (1985) study was selected for purposes of comparison because it had the lowest total dose (60 mg) and would thereby allow the highest potency calculation. Assuming a 10% upper limit of cancer, the minimum potency would be calculated by the ratio 0.1/60.

The International Agency for Research on Cancer (IARC, 1982) concluded that sufficient evidence exists to determine that cadmium is carcinogenic in animals. The IARC was aware of the negative findings following the dietary administration of cadmium chloride by Loser (1980). The marked carcinogenic response of rats to inhalation exposure to aerosols of cadmium chloride was not available to the IARC for consideration, nor were the highly suggestive reports of pancreatic islet tumors following parenteral administration of cadmium chloride (Poirier et al., 1983), and findings of male mammary tumors following intratracheal instillation of cadmium oxide (Sanders and Mahaffey, 1984). Apparently the IARC did not consider the intratracheal induction of mesotheliomas reported by Furst et al. (1973) or the induction of prostate tumors by injections of cadmium chloride into that tissue (Scott and Aughey, 1979). As a result of the newer investigations, together with additional information suggesting that long-term pulmonary clearance and translocation from one site to another in the body is not based on chemical solubility, the carcinogenic risks of exposure to cadmium and its compounds are now seen to be greater than orginally anticipated.

Epidemiologic studies reviewed since the publication of OHEA's Health Assessment Document for Cadmium (May 1981) have not appreciably changed the earlier findings of insufficient evidence of a risk of prostate cancer from exposure to cadmium oxide and fumes. On the other hand, recent evidence of a significant lung cancer risk from exposure to cadmium is available from the Thun et al. (1985) study, in which a greater than twofold excess risk of lung cancer seen in cadmium smelter workers was found to result from cadmium exposure rather than from the presence of arsenic in the plant or increased smoking by the workers. Thun et al. (1985) analyzed both of the above factors (arsenic and smoking) as potential confounders, and presented evidence that these factors, alone or in combination, could not have caused the excess lung cancer risk observed, and that a significant portion of the estimated risk was likely to be due to cadmium. The earlier version of this study, by Lemen et al. (1976), also demonstrated a significantly elevated risk of lung cancer. Lemen et al. (1976) also reported a dose-response relationship with respect to lung cancer and cumulative exposure to cadmium.

Varner (1983), in an updated and enlarged version of the Lemen et al. (1976) study, also found a statistically significant excess of lung cancer. In addition, Varner noted a dose-response relationship for both lung cancer and total malignant neoplasms with increasing cumulative exposure. Varner thought that the significant excess risk of lung cancer was probably due to smoking or to the presence of arsenic in the plant. However, Varner did not analyze the impact of these factors. The Varner (1983) study also suffers from several other limitations, which are described in greater detail in the Epidemiology section of this document.

Sorahan and Waterhouse (1983) noted an unqualified statistically significant risk of lung cancer in their study population via the Standard Mortality Ratio (SMR) method. In addition, a significantly high test statistic was noted for excess lung cancer utilizing the Kneale and Cox "regression models in life tables (RMLT)" method in the "high to moderately exposed" group but not in the "highest exposure" category, although the test-statistic was elevated. Sorahan suggested that the excess might be due to exposure to welding fumes of oxyacetylene. No significantly high test-statistic was found in his "highest exposure" group, however, possibly because of a lack of sensitivity due to small numbers.

In his earlier paper, Sorahan (1981) found the risk of lung cancer to be nonsignificantly elevated through SMRs calculated in a retrospective prospective cohort study of workers who began employment before and after the amalgamation of two factories into a nickel-cadmium battery plant.

Armstrong and Kazantzis (1983) also demonstrated a significant risk of lung cancer in workers designated by them as having worked in "low exposure" jobs for a minimum of 10 years. Little sensitivity remained in the "highly exposed" group with which to detect a risk after a minimum of 10 years' employment, and such a significant risk was not shown. However, a suggestion of an excessive risk was evident in the "ever mediumly" exposed group of workers with a minimum of 10 years of employment. This study, however, does not deal in sufficient detail with latent factors 15 or 20 years after initial exposure in combination with length of employment. The major problem with this study is the distinct possibility that most members of the author's seemingly large cohort of 6,995 were only minimally exposed to cadmium. Only 199 (3%) of his cohort could qualify for inclusion in his "highly exposed" category, which was defined by the author as working in a job which entailed exposure to cadmium that was judged by the author to be "likely in the long term to lead to cadmium urine concentrations of over 20 μg/L." The remaining 6,796 would never have qualified for inclusion in the "highly exposed" category, as a consequence. On the other hand, measured cadmium urine levels exceeded 20 μg/L for 81% of Thun's cohort of 602, but Thun indicated that 100% of his cohort could eventually be expected to exceed "in the long term" a cadmium urine concentration of 20 μg/L.

Holden (1980) reported a significant excess risk of lung cancer in "vicinity" workers, which he maintained could have been due to the presence of other metals such as arsenic. No excess risk was seen in the group with the highest exposure, however, latent factors were not considered, nor was the possible movement of workers within the plant from jobs of high exposure to jobs with low exposure, possibly because of seniority.

Andersson et al. (1982), in their update of the Kjellstrom et al. (1979) study, noted a slight but nonsignificant lung cancer risk in alkaline battery factory workers; however, this observation was based on only three lung cancer deaths occurring to this cohort, and the study also suffers from a "small numbers" problem. In the earlier study, Kjellstrom et al. (1979) observed a slight but nonsignificant excess of lung cancer based on two cases in the same small group of cadmium-nickel battery factory workers.

Kjellstrom's (1982) update of his own 1979 study, however, did not indicate a lung cancer risk. But Kjellstrom's update differed from that of Andersson in that Kjellstrom included 91 additional male workers who had been exposed for less than one year. Kjellstrom cautioned against placing too much credence in this finding, since most of the workers "have had a relatively short exposure duration and latency period."

Inskip and Beral (1982) noted a slightly increased but nonsignificant risk of lung cancer among female residents of two small English villages who presumably were exposed to cadmium-contaminated soil via the oral route. However, again only a small number of lung cancers were observed. Furthermore, evidence of similar cadmium contamination appeared in the soil of the "control" village as well as in the soil of the "exposed" village.

Problems concerning lack of power, no consideration of latent effects, or insufficient evidence of exposure to cadmium characterize the non-positive studies.

Overall, the weight of the epidemiologic evidence is suggestive of a significant risk of lung cancer from exposure to cadmium. The contribution of the confounding factors of smoking and/or the presence of arsenic has been shown by Thun et al. (1985) not to have produced the significant dose-response risk of lung cancer that was found.

Altogether, the epidemiologic data appear to provide limited evidence of lung cancer risk from exposure to cadmium, based on the IARC classification system (Appendix B) and the U.S. Environmental Protection Agency's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1984).

Quantitative Assessment

Since humans are exposed to cadmium dust or fumes, and the rats used for study were exposed to cadmium chloride aerosol, a limitation inherent in the use of such studies for estimating human risk is the possible difference between humans and rats with regard to lung retention of particulates, or between the biological effectiveness of cadmium chloride aerosol administered to rats and the dust and fumes inhaled by workers. Since the data are not clear on this point, assumptions of equal lung uptake and equal effectiveness have been made herein for the purpose of arriving at an assessment of the human risks.

Given these assumptions, combined with other assumptions and conventions used in quantitative risk assessment procedures, the Takenaka et al. (1983) data on lung carcinomas in rats during lifetime inhalation exposures to cadmium chloride aerosol were analyzed. As a result of this analysis, the upper-bound incremental cancer risk to humans who continuously breathe 1 $\mu g/m^3$ of elemental cadmium for a lifetime is estimated to be 9.2×10^{-2}.

Based on respiratory cancer rates from the Thun et al. (1985) study of cadmium smelter workers, and using a linear model that is consistent with the data, the upper-bound incremental cancer risk from lifetime exposure to 1 $\mu g/m^3$ of cadmium in the air is estimated to be 1.8×10^{-3}.

The 95% confidence bound on this estimate, which takes into account only the statistical variability of the cancer rates, gives a range of 3.5×10^{-3} to 1.7×10^{-4}. However, this range does not account for possible deviations of the true (unknown) model from the linear model or of actual exposure from estimated exposure. For example, an empirical threshold model that is also consistent with the observed data gives a unit risk estimate of zero. Even with the uncertainties surrounding the estimate based on human data, it is felt that this estimate is more reliable for environmentally exposed humans than the estimate based on animal data. Further detailed analysis and laboratory studies are needed before the large difference between the estimates based on animal and human data are resolved.

CONCLUSIONS

Cadmium has been tested in a variety of mutagenicity tests with both negative and positive results reported. Because a variety of end points and protocols have been used, a resolution of the apparently conflicting data is not currently possible. Several of the positive results have been observed at concentrations in which some cytotoxicity was apparent, suggesting the possibility that the mutagenic effect of cadmium may be an indirect one. However, the appropriate studies required to resolve this question have not been performed.

A significant dose-response relationship of lung cancer from exposure to cadmium chloride aerosol via inhalation has been found in experimental rats. In addition, significant injection site sarcomas and distant testicular cell tumors have been found in experimental mice and rats exposed to cadmium metal or cadmium salts.

A significant dose-response relationship of lung cancer from exposure to airborne cadmium oxide and fumes has been found in humans that cannot be explained by the potential confounders, arsenic and/or smoking. However, no evidence of a carcinogenic response has been detected in either animals or man from the ingestion of cadmium.

According to the Agency's Proposed Guidelines for Carcinogen Risk Assessment, (U.S. EPA, 1984) cadmium is classified as a Group B1 substance and is thus considered to be a "probable" human carcinogen. Sufficient evidence in animal studies is provided by the findings of lung carcinomas in rats exposed to cadmium chloride aerosol by inhalation, and by injection site and testicular tumors in mice and rats given cadmium metal or cadmium salts. Limited evidence for carcinogenicity of cadmium in humans is provided by the finding of a dose-related increase in lung cancer in humans exposed to airborne cadmium and cadmium compounds that cannot be explained by the potential confounders, arsenic and smoking. Using the IARC classification system (Appendix B), cadmium would be considered a Group 2A substance, indicating again that cadmium is considered to be a "probable" human carcinogen.

An estimate of the carcinogenic potency of cadmium, presuming that it is a human carcinogen, can be developed from both the human and animal inhalation data. The upper-bound incremental unit risk estimate for continuous inhalation exposure at a cadmium concentration of 1 $\mu g/m^3$ ranges from 1.7×10^{-1} to 3.5×10^{-3}, with a most plausible estimate of 1.8×10^{-3}, based on lung cancer from one study of cadmium production workers, although there is uncertainty in these estimates because of the lack of differential exposure in the workplace. Since these estimates are based on human studies, they are regarded as more realistic than the estimate based on the rat inhalation study, which is approximately 51 times higher.

Although there have been no studies showing cadmium to be carcinogenic by the ingestion route, it is estimated that if cadmium is carcinogenic via ingestion, its maximum ingestion potency would be about 1/100 that of inhalation.

Expressed in terms of relative potency, cadmium would rank in the second quartile among the 54 chemicals that the Carcinogen Assessment Group has evaluated as suspect or known human carcinogens.

MUTAGENICITY

Cadmium has been investigated for its mutagenic potential in both prokaryotic and eukaryotic systems. In the former category are assays for gene mutation and reparable genetic damage in bacteria. In the latter category are gene mutation studies in yeast, Drosophila, and mammalian cells; and chromosomal aberration studies in human and other mammalian cells exposed to cadmium both *in vitro* and *in vivo*. The following is an analysis of the literature pertaining to the mutagenic effects of cadmium.

GENE MUTATIONS IN PROKARYOTES

Gene mutation studies that have been conducted in prokaryotic systems are summarized in Table 1. A discussion of each study follows.

Salmonella Assay

Heddle and Bruce (1977) tested the mutagenic effects of cadmium chloride in the histidine reverse mutation assay using *Salmonella typhimurium* tester strains TA100, TA98, and TA1537. The test compound (purchased from ICN Pharmaceuticals, Plainview, New York) was dissolved in water and used at concentrations of 0.05, 0.5, 5, 50, and 500 μg/plate with and without the application of a metabolic activation system (S9 mix) derived from phenobarbital-induced rat liver homogenate. According to these authors, cadmium chloride did not induce a significant mutagenic response over the control value. The criterion set for a positive response was 50%, or a 1.5-fold increase in the revertant frequency over the negative control or spontaneous frequency. Revertant counts were given only for strain TA100; the spontaneous frequency of revertants in this strain was 140 colonies per plate. The purity of the cadmium chloride test compound was not given in this report.

TABLE 1. MUTAGENICITY EVALUATION OF CADMIUM: GENE MUTATIONS IN PROKARYOTES

Test system	Strain	Cadmium compound	Dose	S9 Activation system	Results	Comments	Reference
Salmonella typhimurium	TA98 TA100 TA1535 TA1537 TA1538	Cadmium chloride aqueous solution	0.05 0.5 5.0 50.0 500 μg/plate	Phenobarbital-induced rat liver	Reported as negative	1. Data are not presented clearly as revertants/plate for each strain. 2. Purity of compound not discussed.	Heddle and Bruce (1977)
Salmonella typhimurium	TA98 TA1535 TA1537	Cadmium red in DMSO	1 μg/mL	Aroclor 1254-induced mouse liver	Reported as negative	1. Data provided only for the preincubation or suspension assay. No data on the spot test given. 2. Only a single dose was employed; no dose-response data.	Milvy and Kay (1978)
Salmonella typhimurium	TA1535 TA1537	Cadmium chloride (solvent not specified)	10, 20, 20, 45, 90 mM	Uninduced mouse liver	Reported as negative	1. Spontaneous reversion data and experimental reversion data have not been given in terms of numbers. 2. Used uninduced mouse liver S9 activation system. 3. No positive controls.	Polukhina et al. (1977)

(continued on the following page)

TABLE 1. (continued)

Test system	Strain	Cadmium compound	Dose	S9 Activation system	Results	Comments	Reference
Salmonella typhimurium	TA98 TA100 TA1535 TA1537 TA1538	Cadmium diethyl-thiocarbamate in DMSO	1 5 10 100 μg/plate	Aroclor-induced rat liver	Reported positive for TA1538 and TA98 in the absence of S9 activation. Reported weakly positive both in the presence and absence of S9 activation.	1. Lowest effective dose was 10 μg/plate. 2. Reported positive only for one dose. 3. No dose-response relationship.	Hedenstedt et al. (1979)
Bacillus subtilis rec-assay	H17 Rec⁺ M45 Rec-	Cadmium chloride aqueous solution	0.05 M/plate	None	Reported as weakly (+) positive		Nishioka (1975)
		Cadmium nitrate aqueous solution			Reported as negative		
Bacillus subtilis rec-assay	H17 Rec⁺ M45 Rec-	Aqueous solutions of cadmium chloride, nitrite, and sulfite	0.005 M/plate	None	Reported as weakly (+) positive	1. Compounds were pure.	Kanematsu et al. (1980)

In an abstract published by Kalinina and Polukhina (1977), cadmium chloride was reported to be nonmutagenic in the Salmonella assay. However, important variables such as the number of strains used, the dosage employed, and the number of revertants per plate were not reported. Polukhina et al. (1977) also reported negative results with cadmium chloride on Salmonella typhimurium strains TA1535 and TA1537 both in the presence and absence of an S9 activation system derived from uninduced mouse liver homogenate. In this report a suspension assay with cadmium chloride concentrations of 10, 20, 30, 45, and 90 mM was employed. Positive and negative control data were not presented in this paper, so it is not possible to know whether or not the assay system was functioning properly. The toxicity of the test compound was not reported by these investigators.

Milvy and Kay (1978) studied the mutagenic effects of cadmium red (cadmium sulfide and selenium), a dye used in the printing industry, using the Salmonella spot test (Ames et al., 1973) and the preincubation assay (Ames et al., 1975). Salmonella typhimurium strains TA1538, TA98, and TA1535 were employed in these studies. The test compound (10 μg) was dissolved in 0.01 mL dimethyl sulfoxide (DMSO) and added to 0.9 mL of incubation mixture for 30 minutes at 37°C with shaking before plating 0.1 mL onto minimal plates. Experiments were carried out both in the presence and absence of an S9 activation system derived from Aroclor 1254-induced mouse liver homogenate. Cadmium red was reported to be nonmutagenic in both tests. However, data were presented only for the suspension assay. These investigators used only one concentration, and hence, no dose-response relationship was demonstrated. The toxicity of the compound for each strain was not reported. Consequently, this study may be regarded as inconclusive.

Hedenstedt et al. (1979) studied the mutagenic effects of cadmium diethyldithiocarbamate (used in rubber and plastic industries) in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100. The concentrations used were 1, 5, 10, 50, and 100 µg/plate. The compound was dissolved in DMSO. Concentrations of 50 and 100 µg/plate were toxic in many of these strains. The concentration of 10 µg/plate exhibited mutagenic activity in strains TA1538 and TA98 in the absence of a metabolic activation (S9) system obtained from Aroclor 1254-induced rat liver homogenate (Ames et al., 1975). In TA 1538 the revertent frequency increased more than twofold at 10 µg/plate, i.e., 26.3 ± 3.7 revertants/plate compared to a control value of 11.8 ± 2.6 revertants/plate in the absence of metabolic activation. In the presence of metabolic activation, the revertant frequencies in treated organisms and controls were the same. In TA98, the revertant frequency was 58.8 ± 2.3 at 10 µg/plate (almost a twofold increase) compared to the control frequency of 31.5 ± 4.2 revertants/plate in the absence of metabolic activation. No data were given for studies in the presence of metabolic activation. Positive control data were not presented, although the authors indicated that positive controls were employed in the experiment. Since both cadmium diethyldithiocarbamate and zinc diethyldithiocarbamate were found to be mutagenic in this study, it may not be appropriate to infer that cadmium was the mutagenic moiety.

Mandel and Ryser (1981) reported the induction of frameshift mutations in Salmonella typhimurium TA1537 and missense mutations in Salmonella typhimurium TA1535 by cadmium chloride in concert with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). A concentration of 0.5 mM cadmium chloride facilitated a dose-related increase in the induction of mutation frequency by MNNG that was up to tenfold higher than the control value. This synergism was also noted for the induction of forward mutations to 8-azoguanine (8AG) resistance in the HPRTase locus of these strains.

These studies indicate that cadmium induces mutations in Salmonella typhimurium in a synergistic manner with other mutagenic chemicals. Similar studies have also been reported in rat embryo cultures (Zasukhina et al., 1977).

Escherichia coli WP2 Assay

Venitt and Levy (1974), in a report on the mutagenicity of chromates in the Escherichia coli WP2 mutation system, mentioned that they also tested cadmium compounds for mutagenicity and found them to be negative. These authors did not mention what types of cadmium compounds they employed, nor did they present data to support their negative conclusions.

Bacillus subtilis Rec-Assay

Nishioka (1975) investigated the mutagenicity of cadmium chloride and cadmium nitrate using the rec-assay of Kada et al. (1972). In the rec-assay, which measures reparable DNA damage, differences in growth sensitivities of Bacillus subtilis strains H17 (recombination-competent wild type rec$^+$) and M45 (recombination-deficient rec$^-$) to mutagenic chemicals are measured. When a chemical is more inhibitory to rec$^-$ than to rec$^+$ cells, it is suspected of being mutagenic. Concentrations of 2.5 x 10^{-7} cells/0.1 mL were streaked outward from the center of agar plates. Aqueous solutions of cadmium chloride and cadmium nitrate (0.05 M) were applied in 0.05 mL aliquots to disks of filter paper (diameter 10 mm) and placed in the centers of the plates, at the starting point of the streaks of rec$^+$ and rec$^-$ cells. All of the plates were incubated at 37°C for 24 hours. The degree to which bacterial growth was inhibited was indicated by the relative distance (mm) between the edges of the paper disks and the ends of the bacteria streaks. This inhibition of growth is known as "rec- effect" and is expressed as: no difference between rec^+ and rec^- plates (-), less than 5 mm difference (+), 5-10 mm difference (++), or more than 10 mm difference (+++). Cadmium nitrate showed no difference in growth inhibition (-), whereas cadmium chloride exhibited a weak positive response (+). Each experiment was repeated three times. These experiments did not use a metabolic activation system. The cadmium compounds used were of reagent grade.

Similar results were obtained by Kanematsu et al. (1980) using the rec-assay. Cadmium chloride, cadmium nitrite, and cadmium sulfate were employed at a concentration of 0.005 M in 0.05 mL aqueous solution. All of these compounds exhibited a weak mutagenic response (+) (growth inhibition zones of 4-5 mm). According to these authors, the test compounds used were of the highest purity commercially available.

GENE MUTATIONS IN YEAST

Cadmium chloride has been investigated for the induction of gene mutations in the yeast *Saccharomyces cerevisiae* (Table 2) (Takahashi, 1972; Putrament et al., 1977). Takahashi (1972) studied the induction of petite mutations (p-mutations) and auxotrophs in the *Saccharomyces cerevisiae* heterozygous diploid strain C3116. He treated 10^4 cells with 10 (5.5×10^{-5}M), 12 (6.6×10^{-5}M), and 20 ppm (1.1×10^{-4}M) for 2 days (48 hours) at 25°C. After 2 days of growth, the cell number was determined and the cell suspension was diluted to give a concentration of 2.8×10^{-3} cells per mL. One-tenth of the diluted suspension was spread on the YEPD-agar plate and incubated at 28°C. When small colonies appeared on the plate, they were replica-plated onto YEP-glycerol-agar

TABLE 2. MUTAGENICITY EVALUATION OF CADMIUM: GENE MUTATIONS IN YEAST AND MAMMALIAN CELL CULTURES

Test system	Strain	Cadmium compound	Dose	S9 Activation system	Results	Comments	Reference
Saccharomyces cerevisiae (Yeast) P-mutants and auxotrophs	C3116	Cadmium chloride	10 12 20 ppm	None	Reported as positive	1. P-mutants may not represent true gene mutations because they arise by damage in mitochondrial DNA. 2. Vague protocol.	Takahashi (1972)
Saccharomyces cerevisiae P-mutants	197/2d	Cadmium chloride	8 ppm	None	Reported as negative	1. Only one concentration of test compound was used. 2. This concentration was too toxic for the cells. 3. No mutants observed in the few survivors.	Putrament et al. (1977)
Mouse lymphoma	L5178Y $TK^{+/-}$	Cadmium chloride	0.05 0.06 0.08 0.11 0.15 μg/mL	None	Reported as weakly positive	1. Application of t-test to determine the significance has been challenged by Clive et al. (1981).	Amacher and Paillet (1980)
Chinese hamster cells	Lung (Don) cells; resistance to 8-azoguanine	Cadmium acetate Cadmium chloride	2.5 5 10 μg/mL	None	Reported as positive	1. Very low survival due to high toxicity. 2. Observations not repeated or confirmed.	Casto (1976)
Chinese hamster cells	Ovary cells (CHO)	Cadmium chloride	2.5 5 5 10 μg/mL	None	Reported as weakly positive	1. Data not presented.	Hsie et al. (1978)
Chinese hamster cells	V79	Cadmium chloride	1×10^{-6}M 2×10^{-6}M 3×10^{-6}M	None	Reported as positive		Ochi and Ohsawa (1983)
Mouse lymphoma	L5178Y $TK^{+/-}$	Cadmium sulfate	0.10 0.15 0.20 0.30 μg/mL	None	Reported as positive		Oberly et al. (1982)

medium and minimal medium. After overnight incubation at 28°C, induced p-mutants and auxotrophs were scored. At the dose of 12 ppm (1.1×10^{-4}M), no p-mutants or auxotrophs were found in the 786 colonies counted; at the dose of 10 ppm, 10 p-mutants and 3 auxotrophs were detected in the 871 colonies counted; and at the dose of 20 ppm, there were 12 p-mutants and 9 auxotrophs in 1,182 colonies, indicating that cadmium chloride may be mutagenic. In the controls there were five p-mutants and two auxotrophs in 2,875 colonies counted. According to this paper, however, mutants were induced at dosages of 10 ppm and 20 ppm but not at the dosage of 12 ppm. Such erratic fluctuations in mutation frequency, and the low number of mutants, suggest that the positive results may similarly be questionable. Since p-mutants occur by damage involving mitochondrial DNA rather than nuclear DNA, caution should be exercised in assessing the mutagenic potential of chemicals with this system.

Putrament et al. (1977) also reported a negative result in a test for induction of p-mutation by cadmium chloride in Saccharomyces cerevisiae. The concentration of cadmium chloride tested (8 mM) was very toxic, however, and less than 1% of the cells survived a 6-hour incubation in YEP-glucose medium. No increase of p-mutants was observed, and no data were presented. This study is regarded as inconclusive.

GENE MUTATIONS IN MAMMALIAN CELL CULTURES

Gene mutation studies in cultured mammalian cells have also been summarized in Table 2. A discussion of each study follows.

Mouse Lymphoma Assay

Amacher and Paillet (1980) reported that cadmium choloride (ICN Pharmaceuticals) was mutagenic in the mouse lymphoma L5178Y $TK^{+/-}$ assay. When cadmium chloride, dissolved in normal saline, was tested at concentrations of

2.35×10^{-7}M (cell survival 100 ± 11%), 3.57×10^{-7}M (cell survival 78 ± 24%), 4.5×10^{-7}M (cell survival 62 ± 4%), 6.00×10^{-7}M (cell survival 38 ± 11%), and 8.00×10^{-7}M (cell survival 12 ± 1%), there was a dose-related increase in mutation frequency. The mutation frequencies per 10^4 survivors for the above doses were 0.48 ± 0.01, 0.58 ± 0.06, 0.56 ± 0.05, 0.63 ± 0.16, and 0.68 ± 0.04, respectively. The mutation frequency at the highest nontoxic dosage of 6.00×10^{-7}M was approximately 1.5-fold higher than the control frequency of 0.40 ± 0.03 (survival 100% ± 5). The dose-response curve obtained by Amacher and Paillet (1980) has been criticized by Clive et al. (1981), who claim that the application of a t-test for low numbers of samples to determine significance is misleading.

Oberly et al. (1982) clearly demonstrated the mutagenicity of cadmium sulfate in mouse lymphoma L5178Y gene mutation assay. The test compound at concentrations of 0.10, 0.15, 0.20, and 0.35 μg/mL resulted in mutation frequency increases of 1.7-fold (survival 81%), 4.0-fold (survival 55%), 10.5-fold (survival 12%), and 9.9-fold (survival 4%), respectively, over the solvent control value.

Chinese Hamster Cell Assay

Casto (1976), in a report submitted to Dr. Richard Troast of the Office of Pesticide Programs, U.S. Environmental Protection Agency, stated that cadmium acetate and cadmium chloride are mutagenic in Chinese hamster-lung cells (Don) as determined by induction of mutations that confer resistance to 8-azoguanine. Cells were treated with 2.5 (1.36×10^{-8}M), 5 (2.72×10^{-8}M), and 10 μg/mL (5.45×10^{-8}M) of cadmium acetate and cadmium chloride, respectively, for 18 hours, followed by 48 hours of expression time. Cadmium acetate induced mutation frequencies of 2.8, 50, and 10 per 10^{-6} survivors, respectively, for the above dosages. The survival rate was 0.70%, 0.92%, and 0.43%, respectively. Cadmium chloride induced mutation frequencies of 6, 7, 14, and 37 per 10^{-6} survivors. The negative control rate was 2 per 10^6 survivors. According to this investigation, both cadmium acetate and cadmium chloride are weakly mutagenic. These results are questionable, however, because of the low survival rates at the high concentrations used. Hsie et al. (1978) also reported cadmium chloride to be weakly mutagenic at the HGPRT locus in the Chinese hamster ovary cells, but no data were presented.

Ochi and Ohsawa (1983) investigated the inducibility of 6-thioguanine-resistant (6TG) mutants in the Chinese hamster cell line, V79, by cadmium chloride. They also investigated single-strand scission of DNA by cadmium chloride in these cells. The frequency of 6TG-resistant mutants was found to increase with increased concentration of cadmium chloride. Single-strand scission of DNA by cadmium was detected in combination with proteinase K digestion of the cell lysates, indicating formation of DNA-protein cross-linking by the metal.

Based on the weight of evidence from the data available from both biological and biochemical procedures, and also on the basis of personal discussions with the authors of the above publications, cadmium is regarded as mutagenic in mammalian cell culture gene mutation assays.

STUDIES IN DROSOPHILA AND OTHER INSECTS

Studies on the genetic effects of cadmium in Drosophila are summarized in Table 3. A discussion of each study follows:

Sorsa and Pfeifer (1973) reported that cadmium chloride at concentrations of 1.25 (6.81×10^{-6}M), 2.5 (1.36×10^{-5}M), 5.0 (2.72×10^{-5}M), 10.0 (5.45×10^{-5}M), 20.0 (1.09×10^{-4}M), and 50 mg/L (2.27×10^{-4}M) of media caused signi-

TABLE 3. MUTAGENICITY EVALUATION OF CADMIUM: GENE MUTATIONS AND CHROMOSOMAL ABERRATIONS IN DROSOPHILA AND OTHER INSECTS

Test system	Cadmium compound	Dosage	Treatment period	Results	Comments	Reference
Drosophila melanogaster sex-linked recessive lethal test	Cadmium chloride	50.0 mg/L (2.72×10^{-4}M)	Larvae feeding	Reported as negative	1. Data not presented. 2. Only one dose was used.	Sorsa and Pfeifer (1973)
Drosophila melanogaster larval development sex chromosome loss sex-linked recessive lethal test	Cadmium chloride	65 mg/L 62 mg/L + 3,000 R X-rays	Larvae feeding	Reported as negative	1. Treatment was done in larvae only.	Ramel and Friberg (1974)
Drosophila melanogaster dominant lethal mutations	Cadmium chloride	5 10 20 ppm	Larvae feeding	Reported as positive	1. Dose-response reported. 2. Confirmation of these results in an independent laboratory would be of interest for comparative purposes.	Vasudev and Krishnamurthy (1979)
Drosophila melanogaster sex-linked recessive lethal test	Cadmium stearate	10-20 mg/L 50-100 mg/L 100 mg/L 3 mg/m^3	5-10 days (feeding larvae) 10-12 days (feeding adults) (feeding larvae) (inhalation adult)	Reported as negative	1. Rationale for selecting the dosage not given.	Sabalina (1968)

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TABLE 3. (continued)

Test system	Cadmium compound	Dosage	Treatment period	Results	Comments	Reference
Drosophila melanogaster sex chromosome loss	Cadmium chloride	62 ppm		Reported as negative	1. No data have been been presented.	Ramel and Magnusson (1979)
Drosophila melanogaster sex-linked recessive lethal test	Cadmium chloride aqueous solution	50 ppm	Larvae feeding	Reported as negative	1. Toxicity was determined. 2. Development and survival was affected by cadmium.	Inoue and Watanabe (1978)
Poekilocerus pictus (grasshopper) testis (meiotic chromosomal)	Cadmium chloride aqueous	0.001% 0.01% 0.05% per animal		Reported as positive	1. The effect may be cytotoxic rather than genetic. 2. No controls.	Kumaraswamy and Rajasekarasetty (1977)

ficant delay in the development of larvae as compared with controls. In the sex-linked recessive lethal mutation test (Muller-5 test), only one concentration of 50 mg/L (2.72×10^{-4}M) was used, with no indication of mutagenic response. The number of chromosomes tested and the criteria set for scoring the lethals were not reported, however, and no data were presented to indicate the sensitivity of different stages of spermatogenesis.

Ramel and Friberg (1974), using a dose of 62 mg (3.32×10^{-4}M) of cadmium chloride/L of media, which was the maximum non-lethal dose in the toxicity test, found a delay in larval development. They also studied the induction of sex chromosome loss. In the sex chromosome loss test, a total of 23,360 chromosomes from the treated group and 28,143 chromosomes from the control group were tested. The frequencies of sex chromosome losses were 0.3% and 0.2% for the treated and the control groups, respectively.

The mutagenic activity of cadmium stearate was studied by Yu. A. Revazova (quoted in Sabalina 1968) in *Drosophila melanogaster* using the sex-linked recessive lethal test. Flies were fed a medium containing 10-20 mg (5.45×10^{-5}M to 1.09×10^{-4}M) and 50-100 mg (2.72×10^{-4} to 5.45×10^{-4}M) of cadmium stearate/L substrate for 5-10 and 10-12 days, respectively. The number of sex-linked recessive lethal mutations in 805 chromosomes analyzed was 1 (0.12%) for the 5-10 day treatment, and the number of sex-linked recessive lethal mutations in 2,192 chromosomes examined was 8 (0.36%) for the 10-12 day treatment. When larvae were treated with cadmium stearate concentration of 100 mg/L substrate for 12 days and scored for sex-linked recessive lethal mutants in 380 chromosomes, no mutants were discovered. Cadmium stearate was also administered by inhalation to adult flies for 32 hours (4 hours daily for 8 days). The mean cadmium concentration was 3 mg/m^3. The percentage of sex-linked recessive lethal mutations among the 498 chromosomes was reported to be 0.2%. The control frequency of sex-linked recessive lethal mutations was not provided in the paper. The number of chromosomes tested was not adequate in this study. This study provides no evidence of mutagenicity of cadmium in Drosophila, but the scale of the study was too small to be considered an adequate test even if appropriate controls were presented.

Induction of dominant lethal mutations in Drosophila melanogaster with cadmium chloride has been reported by Vasudev and Krishnamurthy (1979). The doses used were 5 (2.72×10^{-5}M), 10 (5.5×10^{-5}M), and 20 ppm (1.1×10^{-4}M). The frequencies of dominant lethals were 11.8%, 14.3%, and 14.3%, respectively, in 1,244, 1,375, and 1,390 eggs counted. The control frequency was 4.83% in 1,076 eggs counted. These investigators performed the experiment according to the procedure described by Shankaranarayanan (1967) and determined the statistical significance to be at the 5% level, although they did not mention the type of statistical test employed. Based on these observations, this study is evaluated as an indicator of a positive response. A comparable study in an independent laboratory would be of interest for comparative purposes.

Inoue and Watanabe (1978) studied the effects of cadmium chloride in the sex-linked recessive lethal test (attached-X method) in Drosophila melanogaster, Oregon-R flies. In this test, the induction of mutations was measured by the reduction in the proportion of males. The sex ratio (0.528) in the experimental group treated with 50 ppm (2.72×10^{-4}M) was not statistically different from the sex ratio of controls (0.54), indicating that cadmium chloride is nonmutagenic. The dosage selected was a maximally tolerated dose. Both positive (AF-2) and negative controls were used in the experiment.

Ramel and Magnusson (1979) failed to detect nondisjunction and sex chromosome loss in Drosophila following treatment of larvae with 62 ppm (3.32×10^{-4}M) of cadmium chloride. No data were presented; therefore, this study cannot be evaluated.

Chromosomal aberrations were observed in the testes of the grasshopper, *Poekilocerus pictus*, injected abdominally with 0.001% (5.45×10^{-9}M), 0.01% (5.45×10^{-7}M), and 0.05% (2.27×10^{-7}M) cadmium chloride in 0.05 mL volumes (Kumaraswamy and Rajasekarasetty, 1977). Stickiness of chromosomes, bridge formation at anaphase-I, and tetraploidy at metaphase were noted. The test cannot be considered adequate, however, because no controls were used and no tabulated data were presented. The possibility of technical artifacts must also be considered, particularly because chromosomal preparations were made by a squash technique, and no controls were used.

CHROMOSOMAL ABERRATIONS IN HUMAN AND OTHER MAMMALIAN SYSTEMS

Chromosomal damage studies of cadmium, both *in vitro* and *in vivo*, are summarized in Tables 4 and 5. A discussion of each study follows.

Studies on Human Chromosomes in vitro

Shiraishi et al. (1972) tested cadmium sulfide for the induction of chromosomal aberrations in cultured human blood lymphocytes. Lymphocytes from a normal human female were cultured for 72 hours at 37°C. At 8 and 4 hours prior to harvesting, the cultures were treated with cadmium sulfide at a concentration of 6.2×10^{-2}M. Control cultures were incubated similarly, without the addition of cadmium sulfide. Three hours prior to harvesting, cells were treated with 0.02 μg/mL of colcemid to obtain cells in the metaphase stage of mitosis. Chromosome preparations were made with the standard procedure (air-drying technique) and stained with Giemsa stain. Fifty metaphase cells were scored from each treatment group for chromosomal aberrations. The types of aberrations described include chromatid and isochromatid breaks, and

TABLE 4. MUTAGENICITY EVALUATION OF CADMIUM: *IN VITRO* CHROMOSOMAL ABERRATIONS

Test system	Duration of cultures	Cadmium compound	Dosage	Duration of treatment	Activation system	Results	Comments	Reference
Human blood lymphocytes	72 hr	Cadmium sulfide (solvent not specified)	6.2×10^{-2} µg/mL	4 hr 8 hr	None	Reported as positive	1. Blood lymphocytes were derived from only one individual. 2. Only 50 metaphases for each end point were scored. 3. Only one concentration of the test compound was used.	Shiraishi et al. (1972)
Human blood lymphocytes	48 hr 72 hr	Cadmium chloride aqueous solution	5×10^{-5}M 5×10^{-6}M	24 hr 48 hr 72 hr	None	Reported as negative	1. Toxicity was determined. 2. Appropriate dosages used. 3. 100 metaphases scored for each point.	Dekundt and Deminatti (1978)
Human blood lymphocytes	48 hr	Cadmium chloride aqueous solution		48 hr	None	Reported as negative	1. Data were not provided. 2. Concentrations of the test compound not specified.	Paton and Allison (1972)
Cell line WI38 and MCR5	24 hr			24 hr		Reported as negative		
Human blood lymphocytes G_0 stage	48 hr	Cadmium acetate aqueous solution	10^{-8} 10^{-7} 10^{-6} 10^{-5} 10^{-4}M	3 hr	None	Reported as weakly positive	1. No dose-response. 2. Experiments were not repeated to confirm the positive finding.	Gasiorek and Bauchinger (1981)

(continued on the following page)

TABLE 4. (continued)

Test system	Duration of cultures	Cadmium compound	Dosage	Duration of treatment	Activation system	Results	Comments	Reference
Chinese hamster "Hy" cell line		Cadmium sulfate aqueous solution	10^{-4}M	1 hr and harvested at 2,4,6,8, 10,12,15,18, 21,24,27,30, days	None	Reported as positive	1. Colchicine-like effect 2. The type of sera has not been specified. 3. Protocol for chromosome preparation has not been specified.	Rohr and Bauchinger (1976)
Chinese hamster CHO cell line		Cadmium chloride in 0.1 MHCl	2x10^{-6}M	12, 24, 26, and 48 hrs	None	Reported as positive only in the presence of newborn calf (bovine) or human serum. Negative in the presence of fetal calf serum.	1. Threshold dosage was established as 1x10^{-1}M for chromosomal aberration with newborn calf and human sera. 2. Classification of aberration types not given. 3. Active only in the presence of fetal calf serum.	Deaven and Campbell (1980)
Mouse mammary carcinoma FM3A		Cadmium chloride aqueous solution	6.4x10^{-5}M 3.2x10^{-5}M 1.0x10^{-5}M	24 and 48 hrs 24 and 48 hrs 24 and 48 hrs	None	Reported as negative	1. 6.4x10^{-5} too toxic. 2. Experiments were repeated to confirm the results.	Umeda and Nishimura (1979)

TABLE 5. MUTAGENICITY EVALUATION OF CADMIUM: IN VIVO CHROMOSOMAL ABERRATIONS IN HUMANS

Species	Number of exposed workers	Number of controls	Duration of exposure	Duration of culture (hrs)	Number of metaphases analyzed	Results	Comments	Reference
Human blood lymphocytes	14	5	3 months-26 years	48	2800 (exp) 900 (control)	Reported as negative	1. Sample size too small.	Dekundt et al. (1973)
Human blood lymphocytes	40	13	6 weeks-34 years	48	3740 (exp) 1243 (control)	Reported as negative	1. Study was conducted following good cytogenetic procedure.	O'Riordan et al. (1978)
Human blood lymphocytes	7, 12	6, 9	Not given	72	155/ person	Reported as positive	1. The history of the patients, including exposure to other drugs, was not given in these papers.	Shiraishi and Yoshida (1972); Shiraishi (1975)
Human blood lymphocytes from cadmium-exposed workers	5	3	5-24 years	48-72	100/ person	Reported as negative	1. Sample size too small.	Bui et al. (1975)
Itai-Itai patients' blood lymphocytes	4	4		72	100/ person	Reported as negative		
Human blood lymphocytes	24	15	3-6.5 years	48	4800 (exp) 1650 (control)	Reported as positive	1. The possibility of synergistic action of various metals cannot be ignored.	Bauchinger et al. (1976)

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TABLE 5. (continued)

Species	Source of cells	Cadmium compound	Dosage	Duration of treatment	Results	Comments	Reference
Mouse bone marrow	Bone marrow cells	Cadmium chloride	0.06% in diet	30 days	Reported as negative	1. Good technical procedure. 2. Data were anlyzed statistically.	Dekundt and Gerber (1979)
Mouse micronucleus	Bone marrow cells	Cadmium chloride	4 mg/kg/ day	5 days	Reported as negative	1. Number of mice per group was 3. 2. Number of poly-chromatic erythrocytes scored was 300 from each mouse.	Heddle and Bruce (1977)
Rat embryos	Embryonic cells	Kilhman virus Cadmium chloride			Reported as positive	1. Cadmium enhanced the effects of virus. 2. Cadmium alone was ineffective.	Zasukhina et al. (1977)
Mouse dominant lethals	Score dead proportion of implants in the uterus	Cadmium chloride	1.35, 2.7, 5.4 mg/kg	1 day	Reported as negative	1. Standard dominant lethal assay was performed. 2. The entire spermatogenic cycle was covered.	Epstein et al. (1972)

(continued on the following page)

TABLE 5. (continued)

Species	Source of cells	Cadmium compound	Dosage	Duration of treatment	Results	Comments	Reference
Mice dominant lethals	Score dead proportional implants in the uterus	Cadmium chloride	1.75 mg/kg	1 day	Reported as negative	1. All cell stages not sampled.	Gilliavod and Leonard (1975)
Mice (female) dominant lethals	Score dead and live implants in the uterus	Cadmium chloride	2 mg/kg	0.5 to 4.5 days	Reported as negative	1. Experiments repeated three times.	Suter (1975)
Mice heritable translocation	Testicular cells from F_1 males	Cadmium chloride	1.75 mg/kg	1 day	Reported as negative		Gilliavod and Leonard (1975)
Mice (male)	Spermatocytes	Cadmium chloride	0.5, 1.75, 3.0 mg/kg	90 days	Reported as negative		Gilliavod and Leonard (1975)
Mice (female)	Oocytes	Cadmium chloride	3 mg/kg 6 mg/kg	12 hr	Reported as positive	1. Technical problems in processing oocytes not discussed.	Shimada et al. (1976)
Syrian hamsters (female)	Oocytes	Cadmium chloride	1, 2, 4 mg/kg	12 hr	Reported as positive	1. Technical problems in processing oocytes not discussed.	Watanabe et al. (1979)
Mice (female)	Blastocysts	Cadmium chloride	1.5, 3.0 mg/kg	77 hr	Reported as positive for aneuploidy		Watanabe and Endo (1982)

symmetrical and asymmetrical translocations. Increased incidences of chromosomal aberrations, 52% in the 4-hour treatment group and 60% in the 8-hour treatment group, were noted over the control value of 0%. This study utilized a blood sample from only one donor; the history of the donor was not discussed. Since only one concentration of the compound was used, no dose-response relationship is available for this study. In addition, no information was given on the solvent used to dissolve the test compound, and the number of cells scored was small. For these reasons, and because no indication as to the reproducibility of the results was given, this study cannot be regarded as strong evidence for the cytogeneticity of cadmium.

Dekundt and Deminatti (1978) investigated the mutagenic effects of cadmium chloride in cultured human lymphocytes. They treated two batches of cell cultures and analyzed chromosomes as follows: One batch of cultures was treated at 0 hours and at 24 hours after the initiation of cell cultures with 5 x 10^{-5}M and 5 x 10^{-6}M cadmium chloride. Chromosome preparations were made 48 hours after the initiation of the culture, using the standard air-drying technique. In cultures treated 0 hours after the initiation, one hundred metaphases were scored for each dose. There were 3% aberrations (1% aneuploidy, 2% gaps) at 5 x 10^{-5}M, and 7% aberrations (5% aneuploidy, 2% gaps) at 5 x 10^{-6}M. In cultures treated 24 hours after the initiation of cultures, there were 5% aberrations (1% aneuploidy, 4% gaps) at 5 x 10^{-5}M, and 2% aberrations (1% gaps and 1% fragments) at 5 x 10^{-6}M. The control aberration frequency was 5% (3% anueploidy, 2% gaps). The other batch of cultures was treated at 0 hours and 24 hours, and chromosome preparations were made 72 hours after the initiation of cell cultures. One hundred metaphases were analyzed for aberration frequencies from each group. In cultures treated at 0 hours, there were 4% aberrations (3% aneuploidy, 1% gaps) at 5 x 10^{-5}M, and 3% aberrations (3% aneuploidy) at 5 x 10^{-6}M. Cultures treated after 24 hours of initiation exhibited 6% aberrations (2% aneuploidy, 1% fragment, 3% gaps) at 5 x 10^{-5}M, and 4% aberrations (1% aneuploidy, 2% gaps) at 5 x 10^{-6}M. The control frequencies were 1% aneuploidy and 1% gaps. The first batch of cultures exhibited aberration frequencies similar to the control levels. The second batch of cultures, treated only 24 hours after the initiation, exhibited aberration frequencies two to three times above the control levels. These aberrations occurred mostly in the form of aneuploidy and gaps. The significance of chromosomal gaps is not yet understood, and they may not represent true chromosomal aberrations because of their tendency toward restitution. Furthermore, the slight increase in the incidence of aneuploidy may be due to technical difficulties, such as the scattering of chromosomes during the preparation of slides, which tends to result in uneven distributions of cells.

Paton and Allison (1972) exposed human lymphocyte cultures and cultures of the established human cell lines WI38 and MRC5 to at least two concentrations (not specified) of cadmium chloride. The duration of treatment was 48 hours for lymphocytes and 24 hours for WI38 and MRC5. Chromosomal preparations from 100-200 cells were analyzed for aberrations. No aberrations were recorded in treated cells, but because the actual data from the experiment were not given, the study cannot be critically evaluated.

Gasiorek and Bauchinger (1981) exposed unstimulated human blood lymphocytes (G_0) in 1 mL quantities to 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8}M of cadmium acetate for 3 hours. The cells were washed free of cadmium acetate and grown in medium containing fetal calf serum and PHA for 48 hours at 37°C; chromosome preparations were made with the standard air-drying technique. Chromosome analysis of 200 cells per treatment indicated a dose-related increase in the incidence of chromosome gaps. The frequencies of gaps were 0.160, 0.115, 0.135, 0.085, and 0.055 per cell, respectively, for the above doses, as compared to the control frequency of 0.058 per cell. Data were analyzed by the Mann-Whitney rank U-test to compare the incidence of chromosome changes in different samples (significance taken as $p < 0.05$). The frequencies of structural aberrations (chromatid deletions and acentric fragments) were 0.025, 0.010, 0.005, 0.020, and 0.010 per cell, respectively, for the same doses, whereas in controls the frequency of structural aberrations was 0.005 ± 0.005 per cell. Analysis by Mann-Whitney rank U-test indicated that structural chromosome aberrations were significantly higher than in controls, although no dose-response relationship was evident. No metabolic activation system was used. Sufficient numbers of metaphases (200 per dose) were scored, and a standard protocol was employed. Although these data suggest a mutagenic response, the lack of a dose-dependent response makes it important that the results of this experiment be confirmed in another study.

Studies on Rodent Chromosomes in vitro

Rohr and Bauchinger (1976) studied the effects of cadmium sulfate in the Chinese hamster cell line "Hy" using three types of experiments. In a long-term experiment without recovery, cells were exposed to cadmium sulfate at concentrations of 10^{-8} to 10^{-5}M. Chromosome preparations were made following treatment of cells for 16 hours with 0.2 μg/mL of colecemid and hypotonic solution. The 16-hour time period was chosen in order to analyze the cells after exposure during a whole cell cycle. Because concentrations of 10^{-5}M were toxic to cells after 16 hours of exposure, chromosome analysis could not be made. In a short-term experiment without recovery, cells were treated only for 3 hours at a concentration range of 10^{-8} to 10^{-4}M, and chromosome preparations were made without the addition of colcemid and hypotonic solution. This experiment indicated a typical stathmokinetic effect (spindle inhibition) similar to that caused by colcemid. The mitotic index increased with higher concentrations of cadmium sulfate. In a short-term experiment with recovery, a concentration of 10^{-4}M was chosen, and cells grown on coverslips were exposed for 1 hour. Cells with coverslips were washed free of cadmium sulfate, transferred to fresh medium, and grown for 2 to 33 hours. Chromosome preparations were made at 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, and 33 hours after the cells were transferred to the test medium. In all, 500 cells were scored for each recovery period. The incidences of aberrations (0.2 to 0.6% structural and 2.4 to 3.7% numerical) after 2 to 12 hours of recovery were similar to control levels (0.1% structural and 2.4% numerical). Between 15 and 21 hours, the structural aberrations ranged from 10.2% to 22.8%, and the numerical aberrations ranged from 3.0% to 4.9%. The aberration frequencies for the interval of 24 to 33 hours were lower than for the interval of 15 to 21 hours. During this period (24-33 hours), the structural aberrations ranged from 1.2 to 4.4%, and the numerical aberrations ranged from 7.8% to 10.8% (2.4% in controls).

The significance of this study is that cadmium was found to induce numerical chromosomal aberrations by interfering with spindle function. Numerical chromosomal aberrations have been well documented in many forms of cancers. Many chromosomally fragile syndromes, such as Fanconi's anemia, are predisposed for cancer induction.

Deaven and Campbell (1980) studied the effects of cadmium chloride on chromosomes in CHO cells grown in the presence of bovine serum and fetal calf serum. A concentration of 2 x 10^{-6}M cadmium produced 17, 26, 62, and 74% damaged cells, respectively, at 12-, 24-, 36-, and 48-hour analyses of metaphase chromosomes. However, the presence of fetal calf serum and 2 x 10^{-6}M cadmium chloride did not induce growth inhibition or chromosome aberrations. According to these investigators, fetal calf serum appeared to protect the cells from the damaging effects of cadmium, whereas newborn calf serum and human serum actively transported cadmium ions into the cell nuclei, thus damaging the chromosomes. These authors also examined the frequencies of sister chromatid exchanges (SCEs) in cells grown in F-10 containing 15% newborn calf serum at a concentration of 4 x 10^{-7}M cadmium chloride (low to marginal toxicity). The SCE rate was not elevated above control levels (10 SCEs/cell). The range of SCEs was 2 to 18 for cadmium-treated cells, and the range for controls was 4 to 19 per cell. This study is assessed as inconclusive for the reason that the exact role of serum in causing chromosome aberrations is still not known. The importance of these data resides in the fact that virtually all other studies have failed to consider the potential importance of the choice of serum in such experiments.

Umeda and Nishimura (1979) investigated the clastogenic effects of cadmium chloride in FM3A cells derived from C3H mouse carcinoma. Cells were grown in Eagles minimal essential medium supplemented with 10% bovine serum. Cells were exposed to 6.4 x 10^{-5}, 3.2 x 10^{-5}, and 1.0 x 10^{-5}M of aqueous cadmium chloride. After 24 and 45 hours of exposure, chromosome preparations were made and analyzed. One hundred metaphases were scored for each dose. No significant increase in the aberration frequency was noted in treated cultures as compared to control cultures. There were no metaphases in cells treated with 6.4 x 10^{-5}M either at 24 hours or at 48 hours--an indication of toxicity. At 3.2 x 10^{-5}M the aberration frequencies were 2% and 3%, at 24 and 48 hours respectively. At the lowest concentration of 1.0 x 10^{-5}, the aberration frequencies were 1% each for the 24- and 48-hour treatments. The control cultures exhibited 2% aberrations at 24 hours and 1% aberrations at 48 hours. Experiments were performed using accepted procedures. Three concentrations of the test compound were used, and 100 metaphases were scored for evaluation.

Zasukhina et al. (1977) reported increased aberration yields in rat embryos exposed to virus and cadmium chloride. Rat embyro cultures were infected with Kilhman virus, and cadmium chloride (3.5 x 10^{-6}M) was then introduced into the cell cultures. Chromosome preparations were performed 24 hours after the infections. Examination of metaphase cells revealed a 10% aberration rate as compared to a rate of 2% in controls. In control cultures infected with virus only, the aberration frequency was 6%, and in cultures treated with cadmium chloride only, the aberrations frequency was 3%. These results indicate that cadmium chloride enhances virus-induced chromosomal aberrations. The researchers also studied the effect of cadmium chloride on DNA; they reported cadmium chloride-induced degradation with evidence for induction of nonreparable DNA synthesis.

Studies on Human Chromosomes in vivo

Shiraishi and Yoshida (1972) and Shiraishi (1975) obtained markedly positive results from Japanese Itai-Itai patients. The Itai-Itai disease is believed to be induced by cadmium contamination. Analysis of blood lymphocytes from 72-hour cultures derived from these patients exhibited a high rate of chromosomal aberrations (26.7%) compared to the aberration rate in controls (2.6%). Blood cadmium levels were not given. The exposure parameters used in this study are presented in Table 5.

The results obtained by Shiraishi and Yoshida (1972) and Shiraishi (1975) contradicted the results obtained by Bui et al. (1975), who performed chromosomal analysis in four Itai-Itai patients (blood cadmium level 15.5-28.8 ng/g), five Swedish workers exposed to cadmium (blood cadmium level 24.7-61 ng/g), four Japanese controls (blood cadmium level 4.4-6.1 ng/g), and three Swedish controls (blood cadmium level 1.4-3.2 ng/g). The incidences of aberrations after 72 hours of culture were 2.3% numerical and 6.6% structural aberrations in the Itai-Itai patients, as compared with the Japanese controls, in which frequencies of 4.5% numerical and 6.0% structural aberrations occurred--a finding which indicates that no differences existed between the controls and the Itai-Itai patients. In the five Swedish workers exposed to cadmium, chromosomal aberration incidences were 1.0% numerical and 2.0% structural aberrations, while in the three Swedish controls the frequencies were 0.7% numerical and 4.7% structural aberrations, indicating nonmutagenic responses.

The discrepancy between the results of Shirashi and Yoshida (1972) and Bui et al. (1975) in Itai-Itai patients could possibly be due to factors other than exposure to cadmium chloride, such as the time of initiation of cultures after the blood was drawn. In the experiment of Bui et al., the subjects were not exposed to drugs and X-rays, nor did they suffer from viral infections at the time of venipuncture. These factors were not controlled for in the study by Shirashi and Yoshida.

Dekundt et al. (1973) investigated the incidence of chromosomal aberrations in 14 workers who had been exposed to zinc, lead, and cadmium in a zinc smelting plant. The workers were classified into three groups based on degree of exposure. Group 1 consisted of five workers who had been exposed to high levels of zinc (concentrations not specified), low levels of lead (1% w/w of the mineral), and cadmium (concentration negligible). Group 2 consisted of five workers who had been exposed to dust containing high levels of all three metals: zinc (concentration not specified), lead (4% w/w), and cadmium (1% w/w). Group 3 consisted of four workers who had been exposed to mud and dust containing high levels of lead (60% w/w) and cadmium (1% w/w). The control group consisted of three normal individuals. Chromosomal analysis from blood lymphocytes cultured for 72 hours indicated 3.87%, 1.6%, and 2.76% aberrant cells, respectively, in groups 1, 2, and 3, while the control frequency was 1.55%. Since the incidence of aberrations in group 3 was less than that in group 1, it does not appear that cadmium contributed to the frequency of aberrations in this study. The authors' analysis of their data using the t-test also indicated that cadmium exposure did not induce a significant increase in the frequency of aberrations. Blood cadmium levels were not determined in this experiment.

Bauchinger et al. (1976) studied 24 workers (25-53 years of age) exposed to lead (mean blood lead level 1 ± 7 μg/100 mL) and cadmium (mean blood cadmium level 0.40 ± 0.27 μg/mL). The workers were exposed to these metals for approximately 3 to 6.5 years at a smelting plant. Of the 4,800 metaphases scored from lymphocytes cultured for 48 hours, an increase in both chromosomal and chromatid-type aberrations (1.354 ± 0.994%) was noted, in comparison with an aberration frequency of 0.467 ± 0.916% in 1,650 metaphases derived from 15 controls (mean blood cadmium level 0.15 μg/mL). The authors point out that "the observed chromosome aberrations cannot be causally related to cadmium because the workers were also exposed to lead and zinc." Dekundt and Leonard (1975) reported a significant ($p < 0.02$) increase in the incidence of "complex chromosomal aberrations" in a group of 23 men exposed to high levels of cadmium and lead (23.5 to 75.9 μg/100 mL), as compared with controls.

O'Riordan et al. (1978) studied chromosomal aberrations in blood lymphocytes from 40 workers exposed to cadmium salts (chemical names not specified, mean blood cadmium level 1.95 μg/100 mL range < 0.2 to 14.0 μg/100 mL) for a period of 6 weeks to 34 years. In 3,740 cells examined from these workers, four chromatid interchanges were observed. In the control population of 1,243 cells derived from 13 normal subjects (mean blood cadmium level less than 0.2 μg/100 mL in 8 donors and 0.6 to 2.9 μg/mL in 5 donors), no aberrations were observed. Since data were pooled from all of the 40 workers studied, it is not clear whether the four chromatid interchanges came from one exposed worker or from more than one worker. The occurrence of chromatid exchanges, though small in number (4/3,740 cells), does not necessarily indicate a negative response, but does indicate that the study should be considered inconclusive.

Most of these studies of smelting plant workers reflect mixed exposures to cadmium and to other metals such as zinc, lead, chromium, and nickel. Since smelters commonly process relatively crude materials, exposure to these other metals cannot be eliminated as possible contributors to the observed effects.

Studies on Rodent Chromosomes in vivo

Dekundt and Gerber (1979) investigated the in vivo cytogenetic effects of cadmium chloride (3.27×10^{-7}M, 0.06%) in mice. Mice were maintained on a standard diet (1.1% calcium) or on a low-calcium diet (0.03%) for one month. In both cases the diet was supplemented with cadmium chloride. Cadmium chloride did not induce chromosomal aberrations in bone marrow cells significantly above the control level either in the normal or in the low-calcium diet groups. The frequency of aberrations in animals treated with cadmium chloride that were given the standard diet (1.1% calcium) was 2.20%, and the frequency in animals treated with cadmium chloride that were given the low calcium diet (0.03%) was 1.60%. The control frequencies were 1.8% and 2.0%, respectively. The results indicate that cadmium chloride does not induce chromosomal aberrations in mice by this route of exposure.

Micronucleus Assay

The micronucleus assay is based on the fact that chromosome fragments induced by mutagenic chemicals are unable to segregate normally due to lack of centromeres during cell division, and form small nuclei or micronuclei in daughter cells. Heddle and Bruce (1977) studied the ability of cadmium chloride to induce micronuclei in the mouse. Three groups of mice (F_1 of C57BL/6X C3H/He), each group containing three animals, were given daily intraperitoneal injections of cadmium chloride for 5 days with total doses of 1, 6, and 16 mg/kg, respectively. Mice were sacrificed, bone marrow smears were prepared, and 333 polychromatic erythrocytes from each mouse were scored for the presence of micronuclei. No increase in the incidence of micronuclei was observed. In this study, 1,000 cells were analyzed for each dose group (333 cells from each of 3 mice). The spontaneous frequency of micronuclei was 0.5%. An observation of 1% over the control value was considered a positive response. According to these authors, the frequency of micronuclei in the experimental groups did not differ from the control level. These results are presently considered to be inconclusive. The data should be confirmed with larger numbers of animals (10 per dose group) and analyses of at least 2,000 polychromatic erythrocytes per dose group.

Dominant Lethal Assay

The ability of cadmium chloride to induce dominant lethal mutations, which result in the death of fetuses during various stages of development, has been investigated (Epstein et al., 1972; Gilliavod and Leonard, 1975; Ramaiya and Pomerantseva, 1977; Suter, 1975; Sutou et al., 1980 a, b).

Epstein et al. (1972) evaluated the dominant lethal effects of cadmium chloride in ICR/Ha mice. Groups of seven or nine male mice, 8 to 10 weeks of age, were injected intraperitoneally with 1.35, 2.7, 5.4, and 7.0 mg/kg of cadmium chloride in distilled water. Treated males were bred with virgin females 8 to 10 weeks of age. Each male was allowed to mate with three virgin females per week for 8 weeks. Mated females were sacrificed on the 13th day and analyzed for dead (dominant lethals) and live implants. According to these authors, cadmium chloride did not induce a statistically signficant increase in dominant lethal mutations over the control value. This study sampled all germ cell stages, spermatozoa, spermatids, spermatocytes, and spermatogonia.

Gilliavod and Leonard (1975) investigated the dominant lethal effects of cadmium chloride in another strain of mice, BALB/c. One dose of 1.75 mg/kg cadmium chloride was injected into male mice (11-13 weeks of age) through the intraperitoneal route. The treated males were bred with three virgin females every week for 3 weeks. The mated females were sacrificed on the 10th day, and the number of corpora lutea and dead and live implants were counted and compared with controls. No dominant lethal effects were observed in treated or control groups.

These investigators treated the parent male mice with only one acute dose of the test compound. Furthermore, they bred the treated males with normal females for only 3 weeks, which is too short a period of time in which to sample stages of spermatogenesis. The standard method of performing a dominant lethal test is to breed the treated males for 8 weeks. For the above reasons, this report is judged to be inconclusive.

Suter (1975) studied the mutagenic effects of cadmium chloride using the dominant lethal assay in female mice (F_1 progeny of C_3H and C57BLA). According to this investigator, cadmium chloride had no dominant lethal effects in female mice. Female mice of the F_1 (10 x C_3H) stock were injected intraperitoneally with 2 mg/kg cadmium chloride, exposing the germ cells (oocytes) at the dictyate stage of development, and were bred with untreated males for 0.5 to 4.5 days postinjection. Mated females, as evidenced by the vaginal plug, were sacrified 12-15 days later, and the numbers of corpora lutea, total implants, living implants, and percent of dead implants per female were determined. No differences were noted between the treated and control groups. In the treated group, the frequencies of corpora lutea, total implants, living implants, and dead implants per female were 8.2, 7.8, 6.9, and 6.9% respectively, as compared to control frequencies of 7.6, 6.8, 6.4, and 6.1% per female.

Ramaiya and Pomerantseva (1977) investigated the mutagenic effect of cadmium chloride using the dominant lethal test. F_1 hybrid mice (CBA x C57BL) aged 2.5 to 3 months were selected for these studies. Males were given a single intraperitoneal injection of aqueous cadmium chloride solution. Three doses, 1.0, 2.0, and 4 mg/kg, were employed. LD_{50} was determined to be 6.9 mg/kg. Treated males were mated with untreated females for a period of 6 weeks, covering the entire spermatogenic cycle. Dominant lethals, as noted by preimplantation and postimplantation losses and the ratio between the dead and live implants, were recorded. No significant ($p > 0.01$) increases in the dominant lethal frequencies were recorded. These results are regarded as negative since the authors followed appropriate protocols, the dosage selection was based on LD_{50}, and the data were analyzed statistically.

From the above studies it appears that cadmium chloride has no mutagenic potential as measured by the mammalian dominant lethal test. However, the exact nature of the damage that results in dominant lethal effects is not known. The mammalian dominant lethal test is not considered to be a sensitive test for detecting all types of mutagens (Russell and Matter, 1980) because of the high spontaneous levels of dominant lethal events that occur during development.

Heritable Translocation Assay

Gilliavod and Leonard (1975) evaluated the mutagenic effects of cadmium chloride in BALB/c mice using the F_1 heritable translocation assay. Male mice (number not specified) were treated with 1.75 mg/kg of cadmium chloride intraperitoneally, and each treated male was bred with three untreated virgin females once weekly for 3 weeks. The spermatocytes of the resulting 120 F_1 male progeny were analyzed for the presence of heritable chromosomal translocation by standard cytogenetic methods. No evidences of heritable translocation were noted in the spermatocytes of F_1 males. This portion of the study is regarded as inconclusive for the following reasons: Only a single concentration of cadmium chloride was used; treated males were mated for only 3 weeks instead of for 8 weeks; and no experimental controls were used.

Gilliavod and Leonard (1975) also investigated the mutagenic effects of cadmium chloride in BALB/c mice using the spermatocyte assay. Males in groups of 10 were treated with 0.5, 1.75, and 3.0 mg/kg of cadmium chloride intraperitoneally. After 3 months, treated males were sacrificed and spermatocytes (100 cells per animal) in the testes were analyzed for translocations that may have been passed on from treated spermatogonia. No translocations were found in either treated or control animals. The spermatocyte assay is not a very sensitive test and is not commonly employed in mutagenicity tests; therefore this portion of the Gilliavod and Leonard (1975) study is also regarded as inconclusive.

Chromosomal Nondisjunction (Aneuploidy) in Whole Mammals

The effects of cadmium chloride on oocytes of mice (Shimada et al., 1976), on oocytes of Syrian hamsters (Watanabe et al., 1979), and on spermatocytes of mice (Gilliavod and Leonard, 1975) have been investigated.

Shimada et al. (1976) induced superovulation by injecting female mice, ddy strain, with 5 international units (iu) of pregnant mare's serum (PMS) followed 48 hours later by 5 iu of human chorionic gonadotrophin (HCG). Mice were given 3 mg/kg or 6 mg/kg of cadmium chloride 3 hours after the administration of HCG, and were dissected 12 hours after the cadmium chloride administration. Chromosome preparations were made from unfertilized oocytes at the second meiotic metaphase, using the method described by Tarkowski (1966). No structural chromosome abnormalities were found. However, numerical aberrations (aneuploidy) were found to be statistically significant ($p = 0.015$) in the dose group of 3 mg/kg group as compared to controls. The authors postulated that this nondisjunction may be due to the spindle-inhibiting effects of cadmium.

Watanabe et al. (1979), using Syrian hamster oocytes and cadmium chloride, reported even more pronounced incidences of aneuploidy. Cadmium chloride at concentrations of 1.0, 2.0, and 4 mg/kg was injected subcutaneously to groups of 20 female Syrian hamsters 5 hours before ovulation. Matched controls were given equal volumes of normal saline. Females were sacrificed 12 hours after the treatment, and the oocytes were recovered from the ampulla. Analysis revealed that 6 females out of 20 from the 1.0 mg/kg group, 11 females out of 20 from the 2.0 mg/kg group, and 12 females out of 20 from the 4.0 mg/kg group had numerical chromosomal abnormalities, such as hyperhaploidy and diploidy in oocytes, as compared to 3 out of 20 in control females. The results were statistically significant ($p < 0.05$ and $p < 0.01$) in the treated groups as compared to the control group. Cadmium-treated animals were also analyzed for cadmium accumulation in the ovary, using atomic absorption spectrophotometry. The results indicated statistically significant ($p < 0.05$) increases in the accumulation of cadmium in the ovaries of treated females as compared to control females. Both of these results appear to indicate a positive response of cadmium in inducing numerical chromosomal abnormalities in mammalian oocytes.

Watanabe and Endo (1982) analyzed the chromosomes of the blastocysts from mice treated with cadmium at the metaphase 1 stage of oogenesis to determine the effects of cadmium from the oogenesis stage to the preimplantation stage. Female virgin mice of 8-12 weeks of age were induced to superovulate by administering 5 iu of pregnant mare's serum (PMS) followed in 48 hours by 5 iu of of human chorionic gonadotrophin (HCG). Three hours after HCG administration, the animals were injected subcutaneously with 1.5 mg or 3.0 mg/kg body weight of cadmium chloride. Shortly after the treatment with cadmium chloride, they were mated with males of the same age group. About 80 hours after mating, the females were injected intraperitoneally with 4.0 mg/kg of colchicine, and 2 hours later the animals were sacrificed, blastocysts from the uterus were placed into Hanks' balanced salt solution, and chromosome preparations were made. Aneuploid cells were found in 8 out of 65 blastocysts from the group treated with 1.5 mg/kg of cadmium, and 10 out of 63 blastocysts from the group treated with 3.0 mg/kg of cadmium, indicating that chromosomal nondisjunctions induced in oocytes are transmitted to embryos. In the control group, aneuploidy was found in 2 blastocysts out of 59.

All of the above studies strongly indicate that cadmium acts mutagenically to alter the number of chromosomes through spindle inhibition. The concentrations of cadmium used in these studies were similar to those that have been used in cancer bioassays. Supporting evidence that another metal induces chromosomal nondisjunction can be obtained from studies of methyl mercury in Drosophila melanogaster (Ramel and Magnusson, 1979) and in Syrian hamsters (Mailhes, 1983). The occurrence of aneuploidy is well documented in cancer cells. Many chromosomally fragile syndromes, such as Fanconi's anemia, ataxia telangiectasia, and Bloom's syndrome, have been known to be predisposed for cancer induction. Colchicine, the well-known spindle inhibitor, has been used clinically for the treatment of gout. There have been reports that these patients carry numerical chromosomal abnormalities in their blood lymphocytes (Ferreira and Buoniconti, 1968). Epidemiologic studies at the National Cancer Institute (Dr. Robert Hoover, personal communication) are presently being conducted to determine the susceptibility of these types of patients to cancer.

Sperm Abnormality Assay in Mammals

Heddle and Bruce (1977) evaluated the effects of cadmium by means of the sperm abnormality assay. The sperm abnormality assay is based on the observation of increased incidence of sperm heads with abnormal shapes as a result of exposure to chemical mutagens (Wyrobek and Bruce, 1975). Three groups of mice of the genotype (C57BL/6 x C3H/He)F_1, each consisting of three mice, were given daily intraperitoneal injections of cadmium chloride for 5 days with doses of 1, 4, and 16 mg/kg, respectively. After sacrifice of the animals by means of cervical dislocation, sperm suspensions were made from sperm collected from the cauda epididymis. The sperm suspensions were stained with 1% eosin-Y in water, and smears were dried and mounted under coverslips. One thousand sperm heads were evaluated for morphological abnormalities. The background frequency of sperm head abnormalities in the control populations was 1%. Under the conditions of the test, no increases in sperm head abnormalities were observed in the treated group as compared to controls.

CHROMOSOMAL ABERRATIONS IN PLANTS

Levan (1945) reported that treatment of *Allium cepa* root-tips with cadmium chloride induced C-mitosis. This observation was later confirmed by Avanzi (1950), using cadmium chloride concentrations ranging from 2×10^{-6}M to

5×10^{-2}M. Oehlkers (1953) reported that cadmium nitrate induced chromosomal aberrations in Vicia faba. Van Rosen (1953, 1954) reported the genotoxicity of cadmium as evidenced by chromosomal aberrations in the root-tips of plants such as Allium cepa, Beta vulgaris, Pisum abysinnicum, and Vicia sativa. Similar observations were made by Degraeve (1971) in Horedeum sativum and by Ruposhev and Garina (1977) in Crepis capillaris. Aberrations reported in these studies were of both chromatic and chromosomal types, with dose-related responses. Since many of these studies were published in foreign languages, the present report utilizes a summary derived from the review article published by Degraeve (1981).

BIOCHEMICAL STUDIES INDICATIVE OF MUTAGENIC DAMAGE

Some information is available on the effects of cadmium on animals, and although this information cannot, strictly speaking, be considered mutagenicity test data, it may be useful in evaluating the ability of cadmium to reach and damage the gonads. Dixon et al. (1976) reported that cadmium chloride at 2.24 mg/kg, administered intraperitoneally, caused damage to rat testes. A single 10 mg/kg intraperitoneal injection caused selective destruction of rat testes. Cadmium chloride, when administered intraperitoneally at 1 mg/kg, reduced the fertility of male mice at all sperm cell stages except that of spermatozoa (Lee and Dixon, 1973). However, single oral doses up to 25 mg/kg had no effect on the fertility of male rats (Dixon et al., 1976), and cadmium chloride at 0.1 mg/L in drinking water for up to 90 days had no effect on the fertility of male rats. Intraperitoneal injection of cadmium chloride at 1 mg/kg decreased the incorporation of thymidine into spermatogonia in mice (Lee and Dixon, 1973). These authors also observed the binding of cadmium to late spermatids in vivo and in vitro. Friedman and Staub (1976) studied the effects of cadmium chloride on DNA synthesis in Swiss mice. Cadmium chloride at 10 mg/kg inhibited DNA synthesis significantly. An aqueous solution of cadmium chloride was injected intraperitoneally at the above dose into five male mice, and the mice were sacrificed 3.5 hours later. Thirty minutes prior to sacrifice, mice were injected with 10 uCi [^3H] thymidine. Controls received only 10 uCi [^3H] thymidine. Testes were removed following cervical dislocation, DNA was isolated, and the specific activity was determined. Cadmium chloride was found to induce a statistically significant ($p < 0.01$) inhibition of [^3H] thymidine uptake (1.90 ± 0.58) in the testes as compared to controls (7.45 ± 1.44).

Mitra and Bernstein (1977, 1978) reported that when *E. coli* cultures were exposed to 3×10^{-6}M cadmium (Cd^{2+}), 82% to 95% of the cells lost their ability to form colonies on agar plate. Analysis of DNA strands from cells treated with various doses of Cd^{2+} indicated that there was a dose-related increase in the breakage of single-strand DNA. These investigators believe that the loss of viability in cadmium-treated cells is due to the single-strand DNA breakage. Cadmium-treated cells recovered viability when grown in Cd^{2+}-free liquid medium containing 10 mM hydroxyurea.

Sirover and Loeb (1976) investigated the infidelity of DNA synthesis brought about by cadmium chloride and cadmium acetate. Their assay measured the perturbation in the fidelity of DNA synthesis *in vitro* caused by soluble metal salts. Cadmium chloride and cadmium acetate were found to decrease the fidelity of DNA synthesis. Cadmium chloride has also been found to induce concentration-dependent inhibition of RNA synthesis (Hoffman and Niyogi, 1977).

SUMMARY

Cadmium has been investigated for mutagenic activity in both prokaryotic and eukaryotic systems. Gene mutation studies in *Salmonella typhimurium* and

E. coli have produced inconclusive results. In yeast, gene mutation studies have also been inconclusive. In three gene mutation studies (in mammalian cell cultures, mouse lymphoma cells, and Chinese hamster lung and ovary cells) marginally positive responses to cadmium were observed.

Rec-assay in Bacillus subtilis resulted in a weak mutagenic response. In the Drosophila sex-linked recessive lethal test, cadmium was found to be nonmutagenic. The dominant lethal test in Drosophila resulted in a positive response with a dose-response relationship.

The results of chromosomal aberration studies in human lymphocytes from exposed workers and human cell lines treated with cadmium have been conflicting. In Chinese hamster cells, chromosomal aberrations were noted following treatment with cadmium; however, in mouse carcinoma cells, no aberrations were recorded in response to cadmium treatment. In rodents, treatment with cadmium did not induce chromosomal aberrations or micronuclei in bone marrow cells. Similarly, no dominant lethal mutations or heritable translocations were noted in mice treated with cadmium.

The evidence that cadmium interferes with spindle formation comes from both in vitro and in vivo studies in mammals. In in vitro studies using the Chinese hamster cell line "Hy," cadmium induced an effect similar to that of colchicine, which is a known spindle poison. Cadmium also was found to increase numerical chromosome aberrations (aneuploidy) in these cells. Similar results were obtained in studies on aneuploidy in whole mammals. In female mice and Syrian hamsters, cadmium induced chromosomal nondisjunction leading to aneuploidy in germ cells. A recent study demonstrated that the numerical aberrations induced by cadmium chloride in female germ cells of mice are inherited in the embryos.

CARCINOGENICITY

Much of the evidence for the carcinogenicity of cadmium has been reviewed critically in earlier documents (IARC, 1973, 1976; U.S. EPA, 1977, 1981; Sunderman, 1977, 1978; Hernberg, 1977). This section updates findings mentioned previously and discusses recent findings not mentioned in earlier reviews.

ANIMAL STUDIES

Inhalation Study in Rats

A carcinogenicity study of cadmium administered to male Wistar rats by inhalation was reported by Takenaka et al. (1983). The animals were placed in a 225-liter inhalation chamber for exposure to cadmium chloride aerosol. Aerosol was generated by atomizing a solution of cadmium chloride, and airflow through the atomizer was 0.7 L/min. Analytical measurements of cadmium levels were made by collecting aerosol samples in membrane filters in the intake and exhaust of the inhalation chamber. The data in Table 6 show that measured and nominal cadmium levels were quite close. An aerosol centrifuge was used to estimate particle size distribution. Aerodynamic mass median diameters were 0.55 μm with an arithmetic standard deviation of 0.48 μm.

TABLE 6. NOMINAL AND MEASURED CADMIUM CONCENTRATIONS OF CADMIUM CHLORIDE AEROSOLS USED FOR INHALATION

Nominal concentrations	μg/m^3	50.0	25.0	12.5
Measured concentrations	μg/m^3	50.8	25.7	13.4
Standard deviation	μg/m^3	5.9	3.6	2.1
Number of measurements	--	212	220	210

SOURCE: Takenaka et al., 1983.

The animals were initially 6 weeks old and weighed 133 to 135 g. For 18 months, 40 rats per group were continuously exposed to cadmium concentrations of 12.5 $\mu g/m^3$, 25 $\mu g/m^3$, and 50 $\mu g/m^3$. A control group of 41 rats received filtered air during the same period. Following the treatment period, the animals were allowed to survive for an additional 13 months until sacrifice. Body weights were recorded every 3 months during the entire study period. Decedents and survivors were necropsied, and tissues and organs were removed for histopathologic examination. Skulls were decalcified for pathologic evaluation. Samples of liver, lung, and kidney were digested in acid for estimation of cadmium content by atomic absorption spectroscopy.

Differences in body weights (Table 7) and mean survival times (Table 8) among control and treated animals were not statistically significant ($p > 0.05$).

A dose-related increase in the incidence of primary lung carcinomas in treated animals was evident, as shown in Table 8. The first epidermoid carcinoma and the first adenocarcinoma were found at 20 and 22 months, respectively, after treatment commenced. Several treated rats also developed adenomas and nodular hyperplasia in the lung. Metastases to the regional lymph nodes and the kidneys and invasion into the regional lymph nodes and the heart occurred in some rats with lung carcinomas. No lung tumors were found in control animals.

Nonneoplastic lesions and various tumors in other organs were found in both control and treated animals. None of these additional tumor types and nonneoplastic lesions was significantly ($p > 0.05$) different among the four groups.

The data in Table 9 show that cadmium was retained in the lungs, livers, and kidneys of survivors for as long as 13 months after cessation of exposure.

TABLE 7. AVERAGE BODY WEIGHTS OF RATS EXPOSED TO CADMIUM CHLORIDE

Exposure groups	Average body weights (months after the beginning of the inhalation)					
	0	3	7	10	12	15
Control	135.2[a] (4.8)	333.3 (27.4)	385.2 (30.5)	411.6 (31.2)	422.9 (31.7)	425.1 (31.8)
12.5 μg/m^3	135.1 (6.6)	320.9 (29.4)	375.3 (37.1)	405.2 (39.4)	417.2 (41.4)	420.0 (38.8)
25 μg/m^3	133.4 (6.7)	326.6 (28.6)	382.1 (32.1)	410.0 (32.8)	425.7 (35.9)	428.3 (36.1)
50 μg/m^3	133.3 (6.7)	323.5 (29.0)	375.1 (32.2)	403.2 (34.8)	417.0 (36.6)	422.0 (38.5)
	18[b]	21	24	27	30	
Control	434.9 (32.4)	428.2 (31.4)	406.2 (41.3)	405.7 (31.3)	367.3 (39.8)	
12.5 μg/m^3	424.6 (41.0)	421.8 (41.2)	409.5 (45.9)	408.5 (40.9)	372.5 (41.8)	
25 μg/m^3	437.6 (38.1)	441.2 (37.7)	429.2 (45.9)	423.9 (37.6)	375.4 (47.8)	
50 μg/m^3	424.3 (40.6)	424.9 (43.8)	415.2 (42.6)	398.4 (35.8)	357.8 (41.5)	

[a] Mean value (± S.D.).

[b] End of the inhalation.

SOURCE: Takenaka et al., 1983.

TABLE 8. SURVIVAL TIMES AND LUNG CHANGES OF WISTAR RATS AFTER EXPOSURE TO CADMIUM CHLORIDE AEROSOLS

				Number of rats with lung adenomas and carcinomas						
						Carcinomas				
Concentration (µg Cd/m^3)	Initial no. of rats	Survival time in weeks mean value ± S.D.	No. of rats examined histologically	Adenomatous proliferation	Adenomas	adeno-	epidermoid	combined adeno- and epidermoid	mucoepidermoid	Total (%)
Control	41	122±19	38[a]	1	0	0	0	0	0	0
12.5	40	119±17	39[b]	6	1	4	2	0	0	6(15.4%)[e]
25	40	125±15	38[c]	5	0	15[f]	4	1	0	20(52.6%)[f]
50	40	116±23	35[d]	3	1	14[f]	7	1	3	25(71.4%)[f]

[a] Two rats died during the first 18 months; another rat was not examined because of autolysis.
[b] One rat was not examined because of autolysis.
[c] Two rats were not examined because of autolysis.
[d] Three rats died during the first 18 months; two other rats were not examined because of autolysis.
[e] Significantly different from controls ($p < 0.01$) X^2 testing.
[f] Significantly different from controls ($p < 1.0 \times 10^{-5}$) X^2 testing.

SOURCE: Takenaka et al., 1983

TABLE 9. CONCENTRATIONS OF CADMIUM IN LUNGS, LIVER, AND KIDNEYS OF RATS EXPOSED TO CADMIUM CHLORIDE FOR 18 MONTHS (13 MONTHS AFTER THE END OF THE INHALATION)

Exposure groups	No. of rats	Cadmium concentrations ($\mu g/g$ wet weight)		
		Lungs	Livers	Kidneys
Control	9	0.03	0.1 ± 0.1[a]	0.3 ± 0.1
12.5 $\mu g/m^3$	6	5.6 ± 1.0	2.2 ± 0.6	13.5 ± 3.2
25 $\mu g/m^3$	9	4.7 ± 1.5	5.9 ± 1.5	16.4 ± 3.6
50 $\mu g/m^3$	9	10.4 ± 4.2	13.5 ± 3.0	33.6 ± 10.7

[a] Mean value ± S.D.

SOURCE: Takenaka et al., 1983

Analysis of these tissues indicated that cadmium was absorbed and circulated throughout the body and that, although the lung was the target organ for carcinogenicity, the kidney retained the largest amounts of cadmium. Increases in cadmium levels were dose-related in liver in all treatment groups and in lung and kidney in the mid-dose and high-dose groups. Pathologic changes apparently were not observed in kidney and liver, thus suggesting that the cadmium levels found did not have a toxic effect in these tissues.

The authors attributed their success in demonstrating the carcinogenicity of cadmium to: 1) performance of a long-term study using cadmium chloride aerosols that were retained at a rather high level in the lungs after cessation of exposure, and 2) continuous observation of the animals over an extended duration (31 months). Most of the lung carcinomas were detected after the 27th month of the study.

In a pilot study in the same laboratory, four adenomas and one adenocarcinoma were found in 10 rats after 18 months of continuous exposure to a cadmium chloride aerosol (20 $\mu g/m^3$). There was no observation period after the 18-month exposure (Heering et al., 1979). These results fit well with the data obtained in the more detailed study conducted by Takenaka et al. (1983).

In a recent investigation, Greenspan and Morrow (1984) showed that exposure of rats to an aerosol of cadmium chloride at 5 mg cadmium/m^3 for 30 minutes reduced the number of particles phagocytized by the lung macrophages for up to 8 days. At an airborne concentration of 1.5 mg cadmium/m^3 the phagocytization of particles was stimulated. The adhering properties of the phagocytes were reduced at both exposure concentrations for as long as 12 days. The potential of cadmium chloride for altering the normal phagocytic activity could explain why Takenaka et al. (1983) were able to produce such a marked carcinogenic response.

In an earlier study, Hadley et al. (1979) reported one lung tumor among 34 male Wistar rats one year after a single inhalation exposure to 60 μg/L of cadmium oxide for 30 minutes. While this regimen was not adequate for a determination of carcinogenicity, it is noteworthy that the authors of the study observed testicular alterations after this treatment. They pointed out that these changes occurred at doses lower than the minimum effective dose required to induce degeneration with soluble cadmium salts given parenterally if no more than a 20% pulmonary retention is assumed (1.5 μg cadmium/kg for inhalation versus 5-10 μmoles cadmium/kg).

Oberdoerster et al. (1979) compared the lung clearance of cadmium oxide and cadmium chloride after a 45-minute exposure to airborne concentrations of 930 $\mu g/m^3$ and 760 $\mu g/m^3$, respectively. The aerodynamic mass medium diameters were 0.38 and 0.46 μm for cadmium chloride and cadmium oxide, respectively. Despite the differences in chemical solubility, the long-term clearances were equal. The only difference was that cadmium oxide was cleared more rapidly in the first 8 days after exposure. The authors suggested that this might be due to bronchial clearance mechanisms for the less soluble cadmium oxide particles.

Intratracheal Studies in Rats

Sanders and Mahaffey (1984) evaluated the carcinogenicity of cadmium oxide in male Fischer 344 rats. Four groups of 46 to 50 rats each were treated as follows: Group 1 (untreated controls) received one intratracheal instillation of 0.9% sodium chloride solution (the dosing vehicle); Group 2 was given an intratracheal instillation of 25 μg cadmium oxide when 70 days old; Group 3 received intratracheal instillations of 25 μg cadmium oxide when 70 and 100 days old for a total dose of 50 μg; Group 4 was given intratracheal instillations of 25 μg cadmium oxide when 70, 100, and 130 days old for a total dose of 75 μg. The authors stated that the 25-μg dose was 75% of the LD_{50} by the route of administration used. Instilled cadmium oxide had a count median diameter of 0.5 μm. The animals were allowed to survive until spontaneous death. All animals were necropsied, organs were weighed, and tumors, lesions, and major tissues and organs from all of the rats (except 12 lost due to autolysis or cannibalism) were examined histopathologically.

Median survival times were 793, 824, 785, and 788 days for Groups 1, 2, 3, and 4, respectively. Survival times and organ weights (body weights were not obtained) were similar ($p > 0.05$) between control and treated groups. Statistical analysis of tumor data by life-table and contingency table methods revealed no significant ($p > 0.05$) differences among the four groups. Lung tumor findings consisted of adenocarcinomas in two rats of 48 in Group 3 that were killed at 880 days. However, when all cadmium oxide-treated groups were pooled and tested by life-table methods for differences in tumor incidences from the controls (Group 1), a statistically significant ($p = 0.043$) increase in mammary tumors was observed. In addition, the frequency of rats with three or more tumors was increased in the high-dose group ($p = 0.044$). Since cadmium has been shown by Chandler et al. (1976) to inhibit testosterone release and increase circulating levels of leuteinizing hormone, a possible tumor promoter, the finding of increased mammary tumors in the males is more than plausible when one considers the rather high background rate normally found in female rats of this strain.

While cadmium, as cadmium oxide, did not produce lung tumors under the conditions of this study, the protocol used may not have been as sensitive an indicator of the respiratory carcinogenic potential of cadmium as would a design that included lifetime exposures by inhalation, particularly in reference to the carcinogenicity study by Takenaka et al. (1983) discussed herein. Lung tissue was not analyzed for cadmium content in the Sanders and Mahaffey (1984) study. However, clearance of 80% of an intratracheally instilled dose of 15 μg ^{109}cadmium oxide from the lung in male Fischer 344 rats, with an elimination half-life of 4 hours, has been observed (Hadley et al., 1980). In addition, the distribution of the cadmium within the lung was probably not equivalent to that which would have resulted from an inhalation exposure. Oberdoerster et al. (1980) showed, using cadmium chloride, that after a 1-hour nose-only inhalation exposure, 16% more cadmium was deposited in the alveolar area as compared with intratracheal instillation. Hence, a lifetime inhalation exposure to cadmium oxide also might have presented a stronger challenge for carcinogenicity by providing a greater cumulative dose of cadmium within target (lung) tissue.

The increase of mammary tumors observed in the Sanders and Mahaffey (1984) investigation is in keeping with the finding of relatively rapid clearance of cadmium oxide from the lungs and translocation into other tissues following inhalation (Hadley et al., 1979) or intratracheal instillation of cadmium oxide (Hadley et al., 1980). In view of the positive pulmonary findings with cadmium chloride (Takenaka et al., 1983) and less severe but more marked extrapulmonary effects (Sanders and Mahaffey, 1984; Hadley et al., 1979) and increased extrapulmonary tissue concentrations (Hadley et al., 1980) with the chemically less soluble cadmium oxide, the observation of Hadley et al. (1979) that airborne cadmium may constitute a potential hazard to both lung and extrapulmonary tissues is noteworthy. It is necessary, however, to apply caution when the chemical (rather than the biological or the pulmonary) solubility of cadmium salts is used in predicting the behavior of chemicals in complex biological systems. This view is also supported by the work of Oberdoerster et al. (1979), which showed no difference in the long-term lung clearance rate of inhaled cadmium oxide or cadmium chloride.

Furst et al. (1973), as part of a larger investigation of the induction of mesotheliomas by metal in asbestos, performed a preliminary assessment of the effects of intrathoracic injections of powdered cadmium. The test materials, suspended in saline solution, were injected into the right portion of the thoracic cavity through the intercostal muscles. The authors indicated that injection of 3 mg of cadmium once a month for 5 months did not produce any tumors, but was too toxic. The rats treated with cadmium became emaciated and lethargic. In an effort to reduce the toxicity of the cadmium, a second group of five male and five female Fischer 344 rats were injected intrathoracically with 3 mg of cadmium powder and 6 mg of zinc powder in physiological saline once a month for 5 months. The zinc reduced the overt toxicity of the cadmium. At the end of the 10-month experimental period, 3 of the 10 exposed rats had developed tumors, as compared to 0/20 in the controls. The first of these tumors was evident at 120 days after the first injection. The tumors were diagnosed as mesotheliomas, probably malignant. No tumors were observed in the rats treated with zinc only.

Injection Studies in Mice and Rats

Injection of cadmium metal or certain salts of cadmium has been shown to produce sarcomas at the site of the injection, as well as testicular tumors (Leydig cell, interstitial cell) in experimental animals. These studies are summarized in Table 10. The usefulness of subcutaneous injections in determining carcinogenic potential has been discussed by a number of authors, whose conclusions are summarized below.

Grasso and Goldberg (1966) doubted the usefulness of the technique of

TABLE 10. ANIMAL TUMORIGENESIS INDUCED BY CADMIUM INJECTION

Author	Species	Compound	Route	Tumor and incidence
Haddow et al. (1961)	Rats	Ferritin-containing cadmium	s.c.[a]	Sarcomas 8/20 Interstitial cell tumors 10/20
	Mice			Sarcomas 0/20
Heath (1962)	Hooded rats	Cd powder 0.28 g in 0.4 mL fowl serum	i.m.[b]	Sarcomas 2/10 (later in the study 10 more rats developed tumors; the test group they were in was not specified)
		0.014 g in 0.4 mL fowl serum		Sarcomas 3/10
Heath and Daniel (1964)	Hooded rats	Cd powder 0.014 g in 0.4 mL fowl serum	i.m.	Sarcomas 9/10
		0.028 g in 0.4 mL fowl serum		Sarcomas 6/8 (2 were killed early)
Kazantzis (1963)	Chester-Beatty rats	25 mg CdS in 0.25 mL physiological saline	s.c.	Sarcomas 6/10
Kazantzis and Hanbury (1966)	Wistar rats	25 mg CdS in 0.25 mL physiological saline	s.c.	Sarcomas 6/10, 6/26
		50 mg CdS in 0.50 mL physiological saline	i.m.	Sarcomas 5/14
		25 mg CdO in 0.25 mL physiological saline	s.c.	Sarcomas 8/10
		0.25 mL physiological saline alone		Sarcomas 0/10
Haddow et al. (1964)	Rats	0.5 mg $CdSO_4 \cdot H_2O$ in 1.0 ml sterile distilled water once weekly for 10 weeks	s.c.	Sarcomas 14/20; controls 0/15
	Mice	0.05 mg $CdSO_4 \cdot H_2O$ in 0.2 mL H_2O once weekly for 11 weeks		0/20 injection site tumors; controls 0/15

(continued on the following page)

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[a] Subcutaneous.
[b] Intramuscular.

TABLE 10. (continued)

Author	Species	Compound	Route	Tumor and incidence
Roe et al. (1964)	Rats	0.5 mg $CdSO_4.H_2O$ in 1.0 mL H_2O once weekly for 10 weeks	s.c.	Interstitial cell tumors 11/15; controls 0/15
		0.05 mg $CdSO_4.4H_2O$ in 0.2 mL H_2O		Interstitial cell tumors 0/16
Gunn et al. (1963)	Albino mice	0.03 mM/kg $CdCl_2$	s.c.	Interstitial cell tumors 20/26; controls 0/25
	Wistar rats	0.03 mM/kg $CdCl_2$	s.c.	Interstitial cell tumors 17/25; controls 0/25
Gunn et al. (1964)	Wistar rats	0.03 mM/kg $CdCl_2$	s.c.	Sarcomas 9/22; controls 0/18 Interstitial cell tumors 21/24; controls 0/18
Gunn et al. (1967)	Wistar rats	1.8 mg $CdCl_2$	simultaneous s.c. and i.m.	Sarcomas 10/23 Sarcomas 3/26
Knorre (1970)	Wistar rats	0.003 mM $CdCl_2$/100 g b.w.	single s.c.	Sarcomas 6/45
Knorre (1971)	Wistar rats	0.003 mM $CdCl_2$/100 g b.w.	single s.c.	Interstitial cell tumors 10/25
Lucis et al. (1972)	Wistar rats	0.02-0.03 mM/kg $CdCl_2$ in isotonic NaCl solution	single s.c.	Interstitial cell tumors 13/15 Sarcomas 2/15 (two animals died early)
Reddy et al. (1973)	Fischer 344 rats	0.03 mM/kg $CdCl_2$	single s.c.	Interstitial cell tumors 16/20; controls 0/10
Furst and Cassetta (1972)	Fischer 344	5 mg Cd powder (suspended in 0.2 mL synthetic trioctanoin)	2 monthly i.m. injections	Sarcomas 26/50
Favino et al. (1968)	Sprague-Dawley rats	1 mg/100 g $CdCl_2$	single s.c.	Interstitial cell tumors 6/6

(continued on the following page)

TABLE 10. (continued)

Author	Species	Compound	Route	Tumor and incidence
Malcolm (1972)	Rats	$CdCl_2$	s.c.	Sarcomas (?) Interstitial cell tumors (?) (Experiment not completed at time of publication)
Levy et al. (1973)	C.B. hooded rats	0.2 mg $3CdSO_4.H_2O$ in 0.2 mL H_2O	weekly s.c. injection into alternate flanks for 2 yrs	Sarcomas 4/25 Interstitial cell tumors 17/25 1 lung adenoma
		0.1 mg $3CdSO_4.8H_2O$ in 0.2 mL H_2O		Sarcomas 1/25 Interstitial cell tumors 17/25 1 malignant lymphoma
		0.05 mg $3CdSO_4.8H_2O$ in 0.2 mL H_2O		Sarcomas 1/25 Interstitial cell tumors 16/25 1 adenocarcinoma of pancreas
		controls - 0.2 mg H_2O only		Sarcomas 0/75 Interstitial cell tumors 48/75 1 squamous carcinoma of tongue 1 benign liver cell tumor
Scott and Aughey (1979)	Rats	0.05 mL injection into 1 mol $CdCl_2$ prostate		Prostate tumors 17/207
	Rats	0.05 mL 1 mol $CdCl_2$	s.c. five times	Negative for prostate
Poirier et al. (1983)	Wistar rats	7.3 mg/kg $CdCl_2$ in 0.9% NaCl	single s.c.	Sarcomas 14/50 Interstitial cell tumors 39/50
		3.6 mg/kg $CdCl_2$ in 0.9% NaCl		Sarcomas 12/50 Interstitial cell tumors 38/50
		controls - 0.9% NaCl		Sarcomas 0/50 Interstitial cell tumors 13/50

assessing the carcinogenic potential of chemicals on the basis of injection site sarcomas. They did indicate, however, that the development of tumors at sites distant from the injection site was very suggestive of carcinogenic potential in the material under investigation. The testicular tumors produced by the injection of cadmium salts certainly fulfill the criteria set forth by these authors for the assessment of positive carcinogenic potential.

Tomatis (1977) reviewed the appropriateness of the subcutaneous injection route for bioassays of carcinogenicity by comparing it with other routes of administration. He surveyed a number of chemicals tested by the subcutaneous injection route in rodents to see if there was a correlation between the capacities of these chemicals to induce local and/or distant tumors in one species and their capacities to induce tumors by another route in another species. A total of 102 chemicals, which have been reviewed by the International Agency for Research on Cancer (IARC) and have been tested by the subcutaneous injection route as well as by other routes of administration, were surveyed. Of those, 69 were positive for carcinogenic activity when administered by subcutaneous injection and by another route, and 18 were negative or inconclusive whether given by subcutaneous injection or by another route. Nine were positive only when administered by subcutaneous injection, and six were negative by subcutaneous injection and positive by another route. The author concludes that "administration of a chemical by the subcutaneous injection route produced what one could call false negative results for six (5.6%) of the 102 chemicals tested and, if we accept all the criticisms of this route of administration, false positive results for nine (8.7%) of the 102 chemicals tested." Even so, according to the author, it appears that the subcutaneous injection route of administration is not too much worse than any other route of administration.

More recently Theiss (1982) reviewed the IARC data base. He concluded that if a compound produces distant tumors by subcutaneous injection it is almost always tumorigenic by at least one other route of exposure. Theiss recommended that the results of investigations of materials producing tumors at sites other than the injection site should be considered to be as significant as results obtained by routes of administration more relevant to man.

Thus, by all accounts the induction of tumors distant from the injection site is regarded as highly useful in the classification and identification of carcinogens. The work of Chellman and Diamond (1984) provides a possible reason for the consistent induction of cancer following injection of cadmium or its salts at other sites. These investigations showed that in the testes, significant amounts of cadmium were not bound to metallothianein, a protein to which cadmium is normally bound, rendering the metal in the tissues less toxic.

Poirier et al. (1983), in addition to observing increased testicular tumors, showed an increase ($p < 0.02$) in pancreatic islet cell tumors following subcutaneous injection over a 2-year period of cadmium chloride (22/259, 8.5%) as compared to rats not receiving cadmium chloride (3/137, 2.2%) and surviving more than one year, the time to the first such tumor. In the same report, it was shown that simultaneous injections of magnesium acetate prevented the development of injection-site tumors, but had no effect on testicular tumorigenesis. No inhibitory effect was elicited by calcium acetate in the diet, by simultaneous injection, or by magnesium acetate in the diet.

The induction of pancreatic tumors by cadmium chloride is not altogether unexpected, since high concentrations of cadmium in the pancreas of humans and animals have been reported (Fribery and Odeblad, 1957), and the effects of cadmium on carbohydrate metabolism and insulin secretion are well documented

(Ghafghazi and Mennear, 1973).

Oral Studies in Mice and Rats

Schroeder et al. (1964, 1965) conducted two lifetime exposure studies in which Swiss mice were given drinking water containing cadmium acetate at 5 ppm. The purpose of this low exposure level was to simulate the human experience, according to the authors. In the first study, only males experienced decreased longevity in comparison with controls. The mean concentration of cadmium in the kidneys of mice at the end of the study was only 3 μg/g wet weight. This appears to be very low in comparison with the concentrations of 18 μg/g that have been reported in man, and the 13.5 μg/g in rats exposed to 12.5 $\mu g/m^3$ reported by Takenaka et al. (1983). The exposed males had fewer "visible" tumors (1/50) than the controls (11/50), a result ($p < 0.005$) which was possibly related to the shortened lifespans of the exposed males. Only abnormal tissues were histopathologically evaluated. The reduced survival times of the animals, and the limited amount of histopathological evaluation that was conducted, limit the usefulness of this study in the evaluation of the carcinogenic potential of cadmium.

In the second lifetime exposure study by Schroeder et al. (1965), male and female Long-Evans rats ingested cadmium acetate at 5 ppm in water as the sole source of fluid; the treated group developed 28/84 tumors versus 24/70 in controls. The authors stated that "no significant differences appeared among the various groups as to type of tumor." This study, like the authors' 1964 study, was complicated by being performed in a low-metal environment and with a diet low in many trace metals. When the essential trace element chromium (III) was added to the diet of one group of rats that were not given cadmium, they thrived better than the control group and had 34/71 tumors

(Schroeder et al., 1965).

Malcolm (1972), in one experiment, gave male Chester-Beatty hooded rats up to 0.2 mg of cadmium sulfate subcutaneously and up to 0.8 mg weekly by stomach tube for 2 years. In another experiment, he gave Swiss mice doses of cadmium sulfate in distilled water of up to 0.02 mg/kg of body weight subcutaneously at weekly intervals for 2 years. Except for a few sarcomas and Leydig cell tumors seen in the rats given subcutaneous injections (both also seen in the controls), these studies were negative at the time reported.

Experiments with male specified pathogen-free Chester-Beatty hooded rats, using doses of 0.087, 0.18, and 0.35 mg/kg of cadmium as cadmium sulfate in distilled water given by gastric instillation once weekly for 2 years, were carried out by Levy and Clack (1975). Ninety males received 1 mL distilled water on the same regimen, and served as controls. No difference in tumor incidence between exposed and control groups was observed. It is noted, however, that this particular strain of rats has a very high lifetime incidence of spontaneous interstitial cell tumor formation (75% in the untreated control group), such that "if exposure to cadmium had any effect on the incidence of the lesions it was entirely overshadowed by their spontaneous occurrence," according to the authors. Effects on the prostate were especially scrutinized, with no neoplastic lesions observed. Only a limited number of tissues (kidney, spleen, liver, lung, testes, and prostate) were histopathologically evaluated from 10 rats of the high-dose group and 10 rats of the control group.

Levy et al. (1975) similarly gave groups of 50 male Swiss mice 0.44, 0.88, or 1.75 mg/kg/week cadmium sulfate by gavage for 18 months. A group of 150 male mice served as controls. The stated objective of the study was the detection of an increased incidence of prostate tumors attributable to cadmium, but neither that nor any other treatment-related effect was reported at any of the three dose levels. As in the study with rats, the histopathological examination was not sufficiently thorough to make this constitute a compelling negative study. The set of tissues fixed was limited to prostate, urethra, bladder, stomach, kidney, testes, lung, liver, spleen, seminal vesicles, and coagulatory gland, and these tissues were examined microscopically for only 20 of the high-dose and 20 of the control males, along with any abnormal tissues noted macroscopically. Although measurements of cadmium concentration in various tissues were not made, Levy et al. (1975) speculated that the reason no pathological changes attributable to cadmium were observed during the study may have been that absorption of cadmium through the intestinal tract is low.

An unpublished chronic toxicity study of cadmium chloride was conducted at the U.S. Food and Drug Administration (U.S. FDA, 1977). The compilation of animals examined pathologically shows that six groups of Charles River COBS (SD) rats, each consisting of 26 to 32 males and 26 to 29 females, were studied. These groups were given 0 (untreated controls), 0.6, 6, 30, 60, or 90 ppm cadmium chloride in the diet for 103 weeks. Five males and five females per group were sacrificed at 24 and 52 weeks. The remainder were sacrificed at 103 weeks. All animals were necropsied, and tissues, organs, and tissue masses were examined histopathologically. Kidney tissue from five or fewer males in each sacrificed group was evaluated by electron microscopy; sections of liver and kidney from these animals were stained to assess fibrosis, lipid content, liver glycogen, and the basement membrane of tubuli and Bowman's capsules in kidney.

No significant ($p > 0.05$) differences in survival between control and treated groups were reported, and, excluding interim sacrificed animals, no more than two animals per group died before 77 weeks. Results of necropsy and histopathologic and histochemical evaluations did not show treatment-related effects. Electron microscopy, however, revealed dose-related changes in the form of small cytoplasmic lipid droplets in renal tubular epithelium, increased number of residual bodies in renal nephron cells, and swelling and sloughing of cells in distal tubular epithelium and the collecting ducts of the kidney.

A 2-year oral carcinogenicity study of Wistar rats given cadmium chloride was carried out by Loser (1980). Doses of 1, 3, 10, and 50 ppm of cadmium were given in food to 50 male and 50 female rats, with 100 controls of each sex. Food consumption was similar in all the test groups. The mean body weights of treated males were significantly reduced ($p < 0.01$) at the highest dose level. Other than reduced weight in the high-dose males, the male and female treatment and control groups were comparable for weight and mortality. On the basis of a complete histopathological evaluation, the author concluded that there was no significant increase in the incidence of any particular tumor type or in the frequency of tumor-bearing animals.

The reason for the discrepancy between the U.S. FDA (1977) study with regard to the lack of effects of cadmium on body weight at 60 and 90 ppm as compared to the highly significant effect ($p < 0.01$) at 50 ppm is not readily apparent. Strain differences or differences in dietary factors (such as selenium, zinc, copper, or estrogen concentrations) may account for the lack of comparability.

Summary

Chronic exposure of rats to aerosols of cadmium chloride at airborne concentrations of 12.5, 25, and 50 $\mu g/m^3$ for 18 months followed by an additional nonexposed 13-month period produced significant increases in lung tumors. An 18-month exposure to 20 $\mu g/m^3$ also increased lung tumors among exposed rats. A single 30-minute exposure of rats to cadmium oxide did not significantly increase the occurrence of lung tumors in the year that followed. However, increases in mammary tumors and testicular degeneration were observed. The estimated total dose in mg/kg was, however, lower than that producing testicular neoplasia following parenteral administration. It is likely that the potency of cadmium chloride is related to a high degree of bioavailability, due in part to its solubility. On the other hand, the potency of other cadmium compounds cannot necessarily be predicted, since tumor induction may occur with some chemicals despite their relative insolubility.

Intratracheal instillation of cadmium oxide produced an increase in mammary tumors and an increase in tumors at multiple sites among male rats. Intrathoracic injections of cadmium powder are highly toxic, but when their toxicity is reduced by co-administration of zinc, mesotheliomas develop. Intramuscular or subcutaneous injection of cadmium as metal powder, or as chloride, sulfate, oxide, or sulfide, produces injection-site sarcomas and/or testicular interstitial cell (Leydig cell) tumors after necrosis and regeneration of testicular tissue. The results obtained by Poirier et al. (1983) suggest that the incidence of pancreatic islet cell tumors may be increased by administration of cadmium chloride via the injection route. In addition, injection of cadmium chloride into the prostate gland in rats has induced tumors of that tissue. The translocation and long-term pulmonary clearance of cadmium salts do not appear to be related to the chemical's solubility.

Cadmium appears to be much less potent as a carcinogen by ingestion than by injection or inhalation, regardless of the site of cancer induction. For example, the total dose of inhaled cadmium in the Takenaka et al. (1983) study, in which the rats developed a 71% incidence of lung cancer, was about 7 mg ($0.25\ m^3$/day x $0.05\ mg/m^3$ x 365 days/year x 1.5 years). By contrast, in the Schroeder et al. (1965) drinking water study in rats, which had one of the smallest total doses of all of the ingestion studies, a total dose of about 60 mg (5 ppm x 0.5 x 0.35 kg x 730 days) induced no cancer responses. If a 10% upper limit of detection of tumors in the Schroeder et al. (1965) study is assumed, the highest reasonable potency for cadmium via ingestion is about 0.0017 (0.1/60), compared with a potency of about 0.1 (0.7/7) for inhalation. While it is possible that cadmium is not at all carcinogenic by ingestion because of very limited absorption, the negative animal evidence can only set an upper limit on the carcinogenic potency of ingested cadmium, which in the rat appears to be about two orders of magnitude less than for inhalation.

In 1982 the IARC concluded that sufficient evidence existed for the determination that cadmium is carcinogenic in animals. The IARC was aware at that time of the negative findings of Loser (1980) following dietary administration of cadmium chloride to laboratory animals. However, studies reporting a marked carcinogenic response in rats to inhalation of cadmium chloride aerosols were not available to the IARC, nor were the highly suggestive reports of pancreatic islet tumors following parenteral administration of cadmium chloride (Poirier et al., 1983), or the study of male mammary tumors following intratracheal instillation of cadmium oxide (Sanders and Mahaffey, 1984). Apparently the IARC did not consider the intratracheal induction of mesotheliomas reported by Furst et al. (1973) or the induction of prostate tumors by injection of cadmium chloride into that tissue (Scott and Aughey, 1979). As a result of these newer investigations, together with additional information suggesting a distribution not based on chemical solubility, the carcinogenic risks of cadmium and its compounds are now seen to be greater than originally anticipated.

EPIDEMIOLOGIC STUDIES

The epidemiologic studies reviewed here deal specifically with cancer risks resulting from cadmium exposure. Although five of these studies were reviewed in the OHEA Health Assessment Document for Cadmium (U.S. EPA, 1981), they are covered here also for the convenience of the reader.

Potts (1965)

Potts (1965) reported the results of a clinical study of an unstated number of current and former employees of a British alkaline battery factory who were exposed to cadmium oxide dust beginning in 1920 and ending in 1963. In 1946 the manufacture of these batteries was moved to a new location not far from the site of the earlier factory. The first measurements of cadmium dust in the air were made in 1949. At that time, the cadmium content of the air varied from 0.6 to 2.8 mg/m^3 in the platemaking and assembly shops to 236 mg/m^3 in the negative active material department. After the installation of local exhaust ventilation in 1950, cadmium in the air was reduced to less than 0.5 mg/m^3. Improvements to the exhaust system in 1956 further reduced the cadmium dust to less than 0.1 mg/m^3. The policy at the time of the study's publication was to take steps to reduce exposures whenever the measurement of cadmium dust exceeded 0.5 mg/m^3.

Of 70 battery workers for which Potts's clinic had medical records and who were exposed for at least 10 years, proteinuria was observed in 44%. Although no comparison group was provided, this number is probably excessive, since proteinuria is the result of renal tubular dysfunction. A 200-248 µg/day cadmium dietary intake over a 50-year exposure period is required to produce the critical renal cortex concentration associated with renal dysfunction. Only 1% of Americans ingest more than 50 µg/day (U.S. EPA, 1981). However, the author did note that earlier studies of the urine protein of cadmium-exposed workers in this same plant had revealed "similar characteristics" to those of the present study. Four individuals with persistent proteinuria were examined further. Two of them died during the study period. Kidney function tests prior to death revealed no abnormalities, nor were any gross abnormalities observed following microscopic examination of the kidneys of the deceased.

In a second phase of this study, Potts claimed that a "careful search" produced records for a total of 74 men who had been exposed to cadmium dust for more than 10 years. Eight of these men had died. The author did not reveal whether the source of this information was his clinic's medical records or the employment records of the factory, nor did he specify the relationship between these 74 men and the 70 battery workers mentioned earlier. Furthermore, the source of his information on the eight deceased individuals was not given, although presumably it came from his clinical files. Five of the eight deaths were reportedly due to cancer; three of these were cancer of the prostate. The death data from Potts's paper is summarized in Table 11. Whether or not the author made any attempt to determine the vital status of the remaining 66 individuals is unclear. Since all of the deaths occurred in the early 1960s, and nearly all of these individuals had had lengthy exposures, it can be inferred that they had all been exposed to the highest cadmium dust levels that existed at the plant during their years of employment prior to 1950. No information was given on workers exposed for fewer than 10 years.

In the absence of selection bias (a distinct possibility if clinical records were used), the distribution of the eight deaths is striking, as was noted by the author. But because of the possibility of selection bias, the lack of a comparison group, and the unknown ages of the 74 members of this population, it is impossible to determine whether the observation of three prostate cancer deaths is statistically significant. Therefore, this study provides only the suggestion of an association of prostate cancer and exposure to cadmium.

TABLE 11. MORTALITY DATA FOR CADMIUM WORKERS EXPOSED FOR MORE THAN 10 YEARS

Year of death	Age	Length of cadmium exposure (years)	Cause of death
1960	65	31	Auricular fibrillation
1960	75	14	Carcinoma of prostate
1961	65	37	Carcinoma of prostate
1962	63	34	Bronchitis and atheroma
1962	78	18	Bronchitis
1963	53	35	Carcinoma of bronchus
1964	65	38	Carcinoma of prostate
1964	59	24	Carcinomatosis

SOURCE: Potts, 1965.

Kipling and Waterhouse (1967)

Kipling and Waterhouse (1967), in a letter to The Lancet, reported on 246 workers who had been exposed for a minimum of one year to cadmium oxide dust. The authors compared the number of cancers observed from several sites with the number expected from those sites based on incidence rates from the Birmingham Regional Cancer Registry. The number of observed cancer cases of the prostate was significantly greater than expected (4 observed vs. 0.58 expected, $p < 0.003$). Three of the four prostate cancer cases are the same as those reported in Potts's paper (personal communication from Kipling to the IARC in 1976), indicating that some overlapping is acknowledged, and therefore the two studies cannot be said to be independent of each other. No significant differences between observed and expected deaths were found for cancer of the bronchus, bladder, testis, or for cancers of all sites.

Latency period, although obliquely referred to in the letter, is poorly addressed. Furthermore, the letter states that expected cases were calculated by "computing the number of cases of cancer which would be expected to occur in such a group of men of known age" and by excluding the time spent in other jobs or retirement. It is not clear how the latter was to be done; the discussion is sketchy at best. The authors mention that "judging from work in similar fields, fairly short exposure may be sufficient to initiate a tumor." Whether this generalized conclusion can be extended to the specific case of cadmium exposure and cancer remains uncertain. The authors' failure to allow for a sufficient latency period weakens the significance of their findings. Because of these problems and the lack of an adequate discussion of the derivation of expected deaths, the results, although statistically significant, cannot be considered definitive with respect to the carcinogenicity of cadmium.

Humperdinck (1968)

Humperdinck (1968) reported on mortality among 536 people who worked or had worked at an alkaline dry cell battery plant during the period 1949-67 and who had been exposed to cadmium hydroxide and "to a large extent nickel hydroxide." Seventeen of the 536 had died, five from cancer. Of the five who died from cancer, two died from lung cancer, one from liver cancer, one from prostate cancer, and one from cardiac cancer. The length of exposure to cadmium for these cases was: lung, 2.3 years and 9.3 years; liver, 3.5 years;

prostate, 6.4 years; and cardiac, 3.0 years.

There was no comparison group for the 1949-67 time period. However, the author did compare the average of the cancer death rates for the years 1963-66 in the city where the plant is located with the average 1963-66 rate for the whole plant and the average 1963-66 rate for the departments of the plant where there was exposure to cadmium hydroxide. The author did not state whether these rates were age-adjusted, race-adjusted, or sex-adjusted. No differences were found among the three rates or in the proportion of lung cancer deaths between the city population and the plant population. The proportion of lung cancer deaths for the department in which cadmium exposure occurred was not reported.

Previously, Baader (1951) had reported on "20 to 30 males and females" suffering from chronic cadmium poisoning at the same dry cell plant. Of this group, Humperdinck reported that four of eight had died, one of lung cancer; these four are included in the seventeen deaths described previously. No mention is made of any of the other "20 or 30" workers.

Because Humperdinck found no excess cancer mortality among workers exposed to cadmium when compared to the city population or to the plant population as a whole, he concluded that there was insufficient information to establish an association between cadmium and cancer.

A major weakness of this study is that it did not include an appropriate comparison group for the years of the study, 1949-67. Comparison of average death rates for the years 1963-66 among the city, plant, and cadmium departments is not appropriate since it is not known whether all workers in the cadmium departments for the years 1963-66 had experienced a latency period of sufficient duration to have developed cancer. Secondly, there is no indication that the city population or the population of the rest of the battery plant were similar enough to the cadmium-exposed group in terms of race, sex, smoking habits, age, etc. to make these groups objectively comparable. Third, had a proper comparison group been used and an increase in cancer among workers exposed to cadmium been demonstrated, a possible confounding variable would have been the concomitant nickel exposure to which these workers were subjected, since nickel has previously been associated with cancer of the lung, nasal sinus, large intestine, mouth, and pharynx (Fraumeni, 1975).

In conclusion, the study design and methods of Humperdinck render his data inadequate for the assessment of an association between cadmium exposure and cancer.

Holden (1969)

Holden (1969), in a letter to The Lancet, reported on 42 men exposed to cadmium fumes from 2 to 40 years. He stated that six of the men had been exposed to concentrations of cadmium in excess of 4 mg/m^3, and the remainder had been exposed to an average concentration of 0.1 mg/m^3. The author reported that of the 42 men, one developed a carcinoma of the prostate and one developed a carcinoma of the bronchus.

No evaluation of the cancer risk from cadmium can be made on the basis of this letter, since the author did not report important variables such as age, time since first exposure, and smoking history.

Kolonel (1976)

Kolonel (1976) compared the cadmium exposure of 64 cases of renal cancer to 197 nonmalignant digestive disease controls and 72 colon cancer controls. According to the author, "a cancer control group was included to address the problem of potential noncomparability" between cases and controls when a noncancer control group was used. Cases and controls were taken from patients admitted from 1957 to 1964 to Roswell Park Memorial Institute, Buffalo, New York. Cadmium exposure was assessed using data on occupational exposure, cigarette smoking, and dietary intake. A person was considered to have experienced occupational exposure to cadmium only if he had worked for one or more years at a high-risk job in a high-risk industry. High-risk industries included electroplating, alloy-making, welding, and the manufacture of storage batteries. A person was considered to be exposed to cadmium through smoking if he had at least 10 "pack-years" of cigarette use during a lifetime. Dietary exposure to cadmium was determined by applying reports of cadmium content in foods to individual dietary histories based on a frequency recall for a one-week period. An individual was considered exposed through diet if his mean daily intake exceeded the third quartile, determined from the distribution of intakes for the noncancer control group.

The author found that the relative risk of developing renal cancer in occupationally exposed patients who smoked was 4.4 when compared to controls who also smoked and had nonmalignant diseases of the digestive system. This is significant at $p < 0.05$. The risk of developing renal cancer in patients who were occupationally exposed was 2.5 ($p < 0.05$) when compared to colon cancer controls. The latter is not significant ($0.05 < p < 0.10$). Because of the finding of a greatly increased risk* when the effects from smoking and occupational exposure were added together, the author concluded that the effects of smoking and occupational exposure must be synergistic.

The risk of developing renal cancer when consideration is given to cadmium exposure through cigarette smoking only, and separately through diet only (utilizing colon cancer controls), was 1.2 and 1.6, respectively, neither of which was significant ($0.05 < p < 0.10$, two-tailed).

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*Risk in this context is an estimated relative risk derived by use of the odds ratio.

A major criticism of this study is the confounding exposures to other industrial materials in the electroplating, alloy-making, welding, and storage battery manufacturing industries. The author stated that renal cancer resulting from cadmium exposure is biologically plausible because the kidney concentrates cadmium to a greater degree than any other organ. Furthermore, Kolonel pointed out, on the basis of an earlier study by Ellman (1959), that the kidney contains the body's highest concentration of sulfhydryl groups, which are often found in zinc-containing enzymes. Cadmium inhibition of a variety of sulfhydryl-containing enzymes has been reported, the author notes, and this may be the mechanism of action. The kidney concentrates many trace metals, however, and a variety of metals are found in the industries mentioned above, including nickel, lead, and zinc. Also, it is interesting to note that the relative risk for occupational exposure to cadmium is significant ($p < 0.05$) only when compared to noncancer controls, but not significant ($0.5 < p < 0.10$) when compared to colon cancer controls. This indicates that the renal cancer cases may not be comparable to the noncancer cases, and selection bias may have occurred.

Smoking has previously been associated with kidney cancer (Wynder et al., 1974; Schmauz and Cole, 1974; Kahn, 1966; Hirayama, 1977) as well as with cancers of other sites. Although cadmium may be the carcinogen in tobacco smoke that causes kidney cancer, the issue is confounded by the presence in tobacco smoke of many other carcinogens as well. Although the smoke may serve only as a possible synergist or a carrier mechanism for cadmium exposure from other sources, it remains to be demonstrated that cadmium is the agent of concern in smoking.

In conclusion, Kolonel's study provides suggestive, but not sufficient evidence that cadmium is a renal carcinogen. More studies, epidemiologic and animal, are necessary to adequately address the issue.

Lemen et al. (1976)

Lemen et al. (1976) conducted a historic prospective study on 292 white male employees of a cadmium production facility who had worked a minimum of 2 years in the facility at some time during the period from January 1, 1940 to December 31, 1969. Vital status was determined for this group through January 1, 1974. Death certificates listing the causes of death were acquired for 89 of a reported 92 deceased. Some 20 (6.8%) remained lost to follow-up. For comparison, expected deaths by cause were generated through a modified life-table technique based on person-years multiplied by the corresponding age, calendar time, and cause-specific mortality rates for the total U.S. white male population.

The authors stated that the plant was engaged in the production of cadmium metal and cadmium compounds. However, they reported that some lead was also produced. The plant ceased full-scale lead production in 1918 and began to produce arsenic instead. In the early twenties, arsenic production ceased. The plant remained closed until 1926, when cadmium production began. The authors cited an industrial hygiene survey in 1947 that had reported average air concentrations of cadmium fumes ranging from 0.04 to 6.59 mg/m^3 and cadmium dust at 17.23 mg/m^3. It was also reported in that survey that for most operations in the plant, total cadmium air concentrations were less than 1.5 mg/m^3. The present study included a 1973 industrial hygiene evaluation of cadmium dust levels which stated that 8-hour time-weighted average (TWA) gross concentrations of cadmium ranged infrequently up to 24 mg/m^3, but generally remained below 1 mg/m^3. The authors reported, following a 1973 industrial hygiene survey, that an effective respirator program had been instituted at the plant, and had allegedly reduced exposure by a factor of 10. However, it is known that in other occupational settings workers tend to remove respirators because of their inconvenience. Two air measurements taken in the premelt department showed that in addition to air concentrations of 74.8 and 90.3 $\mu g/m^3$ of cadmium, arsenic was measured at 0.3 and 1.1 $\mu g/m^3$. This is about 1% of the cadmium measurement. In the retort department, however, where the cadmium concentration was measured at 1,105 $\mu g/m^3$, arsenic measured 1.4 $\mu g/m^3$, which was about 1/1,000 that of cadmium. On the other hand, analyses of bulk samples revealed 42.2% to 70% cadmium, 3.53% to 6% zinc, 0% to 4.3% lead, and 0.02% to 0.3% arsenic. The remaining ingredients were not identified. The authors concluded that the exposures from the remaining ingredients were insignificant.

A statistically significant excess of total malignant neoplasms (27 observed vs. 17.5 expected, $p < 0.05$) was found, as well as a statistically significant excess of malignant respiratory disease (12 observed vs. 5.1 expected, $p < 0.05$). Without regard to latent effects, an excess of prostate cancer was reported by the authors to be not significant (4 observed vs. 1.15 expected). However, utilizing a one-tailed Poisson variable, the Carcinogen Assessment Group (CAG) found the latter observation to be statistically significant ($p < 0.05$). After a lapse of 20 years from initial exposure, the finding of a statistically significant excess in prostate cancer (4 observed vs. 0.88 expected, $p < 0.01$) was even stronger.

Information concerning exposure and latency of the four prostate cancer cases is given in Table 12. Of the 12 malignant respiratory cancer cases, the cell types of eight were known. Three were squamous cell carcinomas, one was an undifferentiated small cell carcinoma, three were anaplastic carcinomas, and one was an oat cell carcinoma. Unfortunately, smoking histories were not available for members of the cohort in this study. However, it was determined in the later Thun et al. (1985) study that although smoking was more prevalent among the members of this cohort, it could not have caused the significant elevated risk of lung cancer. Furthermore, Lemen et al. reported the presence in the cadmium production plant of other substances, including arsenic, lead, and zinc, that are either known or suspected carcinogens. Any conclusions made from this study regarding the carcinogenic potential of cadmium should be tempered with the knowledge that these other substances were also known to be present in the atmosphere of the smelter. In addition, it is apparent that the authors did not identify all of the constituents of the processed ores, since the percentages given do not add up to 100%.

TABLE 12. PROSTATE CANCER DEATHS AMONG CADMIUM SMELTER WORKERS WITH MORE THAN 2 YEARS EXPOSURE

Case	Age	Exposure	Latency	Date of death
1	71	4	32	2/26/72
2	77	13	25	3/19/68
3	79	18	31	12/10/60
4	64	17	26	4/03/51

SOURCE: Lemen et al., 1976.

However, when consideration is given to the fact that the vital status of 6.8% of the study cohort remains unknown, it is apparent that additional causes of death in this group of 20 people potentially might add a few more cancer deaths to the observed group. In contrast, the expected deaths were overestimated because person-years were counted to the cut-off date for these same individuals.

This study provides support to the supposition that exposure to cadmium is associated with a significant excess risk of prostate cancer and bronchogenic cancer. The other metals known to be present have not been shown to be associated with an elevated risk of prostate cancer. On the other hand, the presence of arsenic in the atmosphere of the smelter, and the possibility of increased smoking among these workers, were potential confounding factors that contributed toward the significant association of bronchogenic cancer and cadmium exposure in the workers. However, in the updated Thun et al. study, the combined effect of smoking and exposure to arsenic was shown not to cause the significant elevated risk of bronchogenic cancer.

McMichael et al. (1976a, b)

McMichael et al. (1976a), as part of a historic prospective study of cancer mortality among rubber workers, followed 18,903 active and retired male workers, aged 40 to 84, for a period of 10 years. They were divided into four separate cohorts, each consisting of workers from the four tire manufacturing plants of the companies under study.

The mortality experience during the 10-year observation period was determined from death claims filed with the companies under the group life insurance policy in effect. In three of the four plants, workers were included if they were employed on January 1, 1964, whereas in the fourth plant they were included if they were employed on January 1, 1963. About 1% were lost to follow-up, and death certificates listing causes of death were obtained for 98% of the deceased. Expected deaths were calculated based on the 1968 U.S. male race- and age-specific death rates. The calculation of standard mortality ratios (SMRs) utilizing such rates produces an underestimate of the risk.

This bias, known as the "healthy worker effect," is a consequence of the selection of the healthiest individuals into a given workforce from the general population from which the expected deaths were derived. Apparently, little turnover occurred in these four plants because the former employees who switched to another place of employment formed the group of 1% lost to follow-up during the 10-year follow-up period.

The total number of deaths equaled 5,160, for an overall SMR of 94. The total number of cancer deaths equaled 1,014 for an SMR of 100, while the SMR for prostate cancer was 119 (103 observed, nonsignificant at $0.05 < p < 0.1$). The authors hypothesized an association of prostate cancer with the compounding and mixing areas of the four plants, work areas that they claimed entailed contact with metallic oxides (including cadmium oxides). The authors also hypothesized an association of prostate cancer with three additional work areas (cement mixing, janitoring, and trucking) of one particular plant after "exploratory work-history" analyses were completed for stomach, bladder, and prostate cancer, lymphosarcoma, and Hodgkin's disease at this plant.

In a similar mortality study of just one of the above four plants, McMichael et al. (1976b) confirmed a significant excess risk of prostate cancer (SMR = 140, observed = 53, $p < 0.05$) in 6,678 male rubber workers, and found that the risk was associated with the calendering, janitoring-trucking, compounding, and mixing occupational groups. He stated that cadmium compounds were used as vulcanization (curing) accelerators in these broad occupational groups. The method of classifying workers utilized by McMichael et al. is discussed further in a later critique by Goldsmith et al. (1980).

The object of the earlier McMichael et al. (1976a) study was not to single out the association of prostate cancer with cadmium exposure as the main topic of study, but rather to examine site-specific cancer mortality, in general, in rubber workers. Hence, the authors found excesses in cancer mortality at a number of different sites, but did not test the significance of any of these excesses. Data from the McMichael et al. (1976a) study are summarized in Table 13. The tests of significance were calculated by the CAG using the method of Chiang (1961).

One major problem with this study is that rubber workers are potentially exposed to numerous organic and inorganic chemicals, some of them known or suspected carcinogens, including benzene, which is a known human carcinogen. The SMRs may thus be confounded by additional exposures to chemicals other than cadmium. Exposure levels for the many different compounds found in these plants are not given.

A second problem with this study is the relatively short observation time (10 years) from the beginning of the study to its cut-off date. This is an insufficient period in which to assess latent effects, and in fact, no data are presented in which latency is considered. This cohort should be followed for several additional years before a final conclusion is made regarding carcinogenic effects resulting from exposure to cadmium. While the paper is of interest as a basis for further studies, it does not provide adequate evidence for the association of cadmium with prostate cancer.

Monson and Fine (1978)

In another mortality and morbidity study of cancer in 13,570 white male rubber workers (Monson and Fine, 1978), an elevated risk of prostate cancer was noted (4 observed, 0.04 expected, $p < 0.05$) in two unrelated departments, material conservation and final finish. In no other department of this plant was an elevated risk of prostate cancer evident. However, the authors do not attribute this excess risk to any common exposure in these departments, except

TABLE 13. STANDARD MORTALITY RATIOS (SMRs) BY SITE

Site	Observed deaths	SMRs	Probability of occurrence[a]
Lymphatic leukemia	20	158	0.039
Stomach	80	148	<0.001
All leukemias	46	130	0.073
Hodgkin's disease	32	129	0.150
Prostate	103	119	0.077
Colon	103	116	0.131
Pancreas	57	103	0.826
Bladder	32	92	0.638
Respiratory	252	85	0.002
Rectum	27	82	0.303
Brain, central nervous system	14	78	0.352
All cancer	1014	100	1.000
All causes	5106	94	<0.001

[a] Taken from Chiang (1961).

SOURCE: McMichael et al., 1976a.

possibly to oils used in machine maintenance. The authors claim that cadmium exposure was not "appreciable" in this plant. Data on the U.S. white male population provided the comparison population for the expected prostate cancer deaths. This study, which uses the same plant that was studied earlier by McMichael et al. (1976a, b) and later by Goldsmith et al. (1980), does not support the hypothesis suggested by McMichael et al. that cadmium in the plant was responsible for the excess risk of prostate cancer.

Kjellstrom et al. (1979)

Kjellstrom et al. (1979) reported on a historic prospective cohort study of 269 male Swedish cadmium-nickel battery factory workers and 94 Swedish male cadmium-copper alloy factory workers having more than 5 years exposure since the factories began production. As an internal reference group, the study also included 328 alloy factory workers who had been employed in the alloy factory for at least 5 years but had not been exposed to cadmium. It was estimated that the average cadmium levels for one of the two factories were as follows: in excess of 1 mg/m^3 prior to 1947, 200 $\mu g/m^3$ between 1962 and 1974, 50 $\mu g/m^3$ in 1974, and below 5 $\mu g/m^3$ at the time of the study. At the other factory, concentrations were in the range of 100 to 400 $\mu g/m^3$ in the mid-1960s and 50 $\mu g/m^3$ in 1971 and after. The battery study population was also exposed to nickel hydroxide dust.

National average age- and cause-specific death rates and cancer incidence rates were used to generate expected deaths and expected new cancer cases in the two study groups. New cases of cancer were found in the battery factory by matching the names of the 269 workers with those of the Swedish National Cancer Registry. This was not done with the alloy factory workers. With respect to mortality in the battery factory, 43 deaths occurred between 1949 and 1975, of which 8 were due to cancer. This contrasts with 67 expected total deaths during the same period. No further breakdown is given of the cancer deaths, and no expected cancer mortality is given. However, the authors state that there was no increase in "general" cancer mortality. Furthermore, the total number of new cases of cancer equaled 15 during the period from 1959 to 1975, while the expected number of new cases equaled 16.4, based on incidence data provided by the Swedish National Cancer Registry. A breakdown by site is given in Table 14. Only cancer of the nasopharynx was found to be significantly in excess (2 observed vs. 0.2 expected, $p < 0.05$) possibly due to exposure to nickel dust.

In the alloy factory, only "preliminary" calculations of prostate cancer mortality were done; cause-specific mortality and incidence were not examined in these workers. Among 94 exposed workers, four prostate cancer deaths were noted versus 2.69 expected ($p = 0.29$). In the reference group of 328 unexposed workers, four prostate cancer deaths were noted versus 6.42 expected ($p = 0.23$) (Table 15). A corrected "healthy worker effect" risk ratio was derived by dividing the risk of developing prostate cancer in the exposed group by that of the reference group. The resulting ratio was 2.4 ($p = 0.087$), which is still nonsignificant. Although the results of these two studies are not significant with respect to prostate cancer, and are basically inconclusive because of the small study groups, they do suggest a positive association of prostate cancer and exposure to cadmium.

Two problems with this work are apparent. The first is that terminated employees were apparently not included in any of the study cohorts unless they had died. The resulting cohorts are healthier than the general population because former employees, who would be expected to carry the greatest burden of potential disease, are not represented. These employees are represented in the general population's death rates, however. The net result is to overestimate

TABLE 14. EXPECTED AND OBSERVED NEW CASES OF CANCER BETWEEN 1959 AND 1975 IN THE WHOLE GROUP OF BATTERY FACTORY WORKERS (N = 228)

	Cancer cases		
Site	Expected[a]	Observed	Risk ratios
Prostate	1.2	2	1.67
Lung	1.35	2	1.48
Kidney	0.87	0	0
Bladder	1.07	1	0.93
Colon-rectum	2.25	5	2.22
Pancreas	0.60	0	0
Nasopharynx	0.20	2	10.0[b]
Other	9.81	3	0.31
All sites	16.4	15	0.91

[a] Expected deaths based on Swedish National Cancer Registry.
[b] Statistically significantly greater than 1 ($p < 0.05$).

SOURCE: Kjellstrom et al., 1979.

TABLE 15. CUMULATIVE EXPECTED AND OBSERVED NUMBER OF PROSTATIC CANCER DEATHS FROM 1940 TO 1975 AMONG ALLOY FACTORY WORKERS

	Prostatic cancer deaths			
	Expected	Observed	Risk ratios	P value
Exposed group	2.69	4	1.49	0.29
Reference group (N = 328)	6.42	4	0.62	0.23

SOURCE: Kjellstrom et al., 1979.

the expected deaths, thus masking the potential risks to battery workers.

The second problem is that, because the Swedish National Cancer Register was not established until 1959, the study's incidence data would not have included cancer cases occurring in the 1950s, thus leading to an underestimation of new cancer cases.

Another potential source of selection bias would be the exclusion of all members with incomplete information in the factory files. However, since there is no reason to assume differential selection of subjects for study through this procedure, it may not be a problem.

Goldsmith et al. (1980)

In a later case-control study by Goldsmith et al. (1980) of prostate cancer in one of the four tire and rubber manufacturing plants studied earlier by McMichael et al. (1976a, b), an excess risk of prostate cancer could not be directly attributable to cadmium because no evidence could be found that cadmium was used regularly in the study plant. The authors identified some 88 cases of prostate cancer from death certificates in the years 1964 to 1975. These were matched with 258 controls on the factors of age, race, and date of entry into the plant. Only the batch-preparation work area produced a statistically significant risk ratio ($p < 0.025$) over the exposure periods of (1) more than a month, (2) more than 24 months, and (3) more than 60 months. No identifiable use of cadmium was noted by the authors in this work area. The methods employed in this study, i.e., the technique of grouping employees according to general production areas called occupational title groups (OTGs) for analysis of work history data, tend to result in distorted risk estimates of the carcinogenic potential of substances to which individuals might be exposed in the workplace. In any given OTG, employees who may never have been exposed to any potential carcinogen are lumped together with employees who were exposed to one or more substances, some of which might be classified as potential carcinogens. It becomes difficult to attribute a significant risk ratio to any particular substance in question under these circumstances. Furthermore, since this was a study of only one of the four original plants, the possibility remains that cadmium might have been used in the remaining three plants. Further investigatory work must be done to identify any and all uses of cadmium in the three remaining study plants. It might have been more appropriate to conduct case-control studies of prostate cancer in all four study plants. Instead of using "assignment to particular OTGs" as an indicator of excess risk, it would have been more appropriate to use direct evidence of exposure to cadmium as the dependent variable of interest. Similarly, a case-control study of lung cancer and risk of exposure to cadmium might also be initiated in the rubber industry.

This study does not support the earlier McMichael hypothesis that the excess risk of prostate cancer might have been due to exposure to cadmium compounds used as vulcanization accelerators. Some questions remain, however, about the choice of the study population and the use of OTGs in assessing exposure.

Holden (1980)

Holden (1980) reported the results of a preliminary cohort mortality study of workers in a British cadmium factory who were employed at some time between August 1940 and August 1962, and were followed until December 31, 1979. Iron and brass foundry workers in a second factory served as controls. The cadmium factory data were subdivided by the author into two parts for purposes of analysis. One end of the building contained the cadmium-copper alloy department, where 347 men worked for a minimum of 12 months. Another 624 men worked for a minimum of 12 months in the remainder of the factory. The latter group was dubbed "vicinity" workers by the author because they worked in the same building with, but not directly in, the cadmium-copper alloy department. Another 537 brass and iron workers were employed in the second British factory for a minimum of 12 months, and their social and physical environments were reported by the author to be similar to those of workers in the first factory.

Industrial hygiene surveys carried out at the cadmium factory in 1953 and 1957 showed the mean level of airborne cadmium in the cadmium-copper alloy department to be 70 g/m^3 (S.D. = 62 g/m^3), based on 12-hour sampling, while the mean level in the other parts of the building (the "vicinity") was 6 g/m^3 (S.D. = 8 g/m^3). The author reports that vicinity workers were exposed to considerably less cadmium than were the cadmium-copper alloy workers. Actually, neither figure represents a substantial exposure. Follow-up was over 95% complete on all three subcohorts. Expected deaths were generated on the basis of death rates for England and Wales in 5-year age intervals.

A statistically significant elevated risk of dying from all causes (observed = 158, SMR = 112) was evident in the cadmium-copper alloy workers. This excess was not due to malignant neoplasms. The excess risk remained when malignant neoplasms were excluded (observed = 122, SMR = 113). Mortality from neoplasms was not significant in the cadmium-copper alloy workers, except for leukemia (observed = 3, SMR = 441, $p < 0.05$). The author contends that the excess risk observed overall in the study was due to deaths from pulmonary disease. On the other hand, a statistically significant elevated risk of cancer in general (observed = 72, SMR = 120) was apparent in vicinity workers, due chiefly to significant excesses of cancer in two sites: the lung (observed = 36, SMR = 138, $p < 0.05$) and the prostate (observed = 8, SMR = 267, $p < 0.01$). The author attributed the elevated risk of lung cancer in these workers to the presence of metals other than cadmium, including arsenic. The vicinity workers were reported by the author to have been involved in the manufacture of arsenical copper, and during its refining, to have been exposed to silver and nickel. However, no environmental measurements are reported to have been taken of any of these other metals anywhere in the building in which both groups worked. It was reported by the author that a "considerable evolution of cadmium oxide fumes" resulted when cadmium was dumped into the much hotter molten copper to form cadmium-copper alloy. This effect resulted because cadmium boils at a much lower temperature than that of copper.

With respect to prostate cancer, the author indicated that there was an absence of a dose-response relationship since five of the eight prostate cancers occurred to individuals who were exposed for less than 15 years. Of these five, three were exposed for only one year, if it is assumed that "years of exposure" means years of employment throughout the entire plant. The author attributes only three of the prostate cancer deaths to cadmium exposure because the remaining five were exposed for a "relatively short time." This last observation is somewhat strong in view of the fact that every prostate cancer death occurred 15 or more years following initial exposure.

Furthermore, since the author has "an integrated exposure and work schedule history on each man" (comments of the Cadmium Council, Inc., 1984) a better way to establish whether or not a dose-response relationship exists is to develop a cumulative exposure index for each member of the cohort so that change in risk could be related to increasing cumulative dosage, as in Thun et al. (1985) or Varner (1983).

Latency as a factor was not considered in calculating expected deaths, so that the actual risk of prostate cancer may have been greater in vicinity workers. With respect to the risk of prostate cancer in the cadmium-copper alloy cohort (observed = 1, SMR = 63), the numbers involved are too small to warrant the author's finding of no excess risk. In addition, if both the cadmium-copper subcohort and the vicinity workers are re-evaluated after 15 years of latency, the chance of detecting a significant prostate cancer risk in the cadmium-copper workers is probably nonexistent, while at the same time, a better estimate of the risk of lung cancer attributable to cadmium exposure in both subcohorts might be had.

It should be noted that the work force of any factory may be rotated many times during the factory's operating life. The fact that cadmium-copper alloy workers, under the author's definition, apparently experienced a lower risk of prostate cancer than did "vicinity" workers may not be unexpected, since it is possible that many of the eight cases may have worked in the cadmium-copper alloy department as well as in the remaining part of the plant at some time during their working careers.

The observed risk of cancer may actually be greater than calculated because of the presence of the "healthy worker" effect, in which less than expected mortality is seen in the control group not only in the overall risk of death from all causes (observed = 95, SMR = 88), but also with respect to the risk of cancer (observed = 21, SMR = 83). If latency had been considered in this study, this confounding effect could have been eliminated.

Because of the preliminary nature of the findings of excess lung and prostate cancer in "vicinity" workers, and further questions that need to be answered regarding the extent of exposures to cadmium, the findings of an excess risk of prostate cancer in these workers should be regarded only as suggestive. The finding of an excess risk of lung cancer due to cadmium exposure must also be considered only suggestive at this time because of the possible confounding effects of smoking and of exposure to other metals such as arsenic. A greater effort should be made to assess the impact of these confounders and to evaluate the possibility of a dose-response relationship.

Sorahan (1981)

Sorahan (1981), in a preliminary report to the Third International Cadmium Conference, related the findings of a historic prospective mortality study of 3,026 nickel-cadmium battery workers first employed during the period 1923 through 1975 and still alive in 1946 but followed to June 30, 1980, and who had worked at least one month. A subset of these same workers had been studied earlier by Kipling and Waterhouse (1967). The Sorahan (1981) cohort was derived from workers who had been employed in two separate factories, which were amalgamated in 1947. The earliest mention of cadmium in the air breathed by these workers was reported in 1949. In the platemaking assembly shops, the cadmium content in the air ranged from 0.6 to 2.8 mg/m^3, but in the "negative active material" department, where cadmium oxide powder was prepared, the levels were reported to be "considerably higher," although no numbers were provided. Extensive local exhaust ventilation was installed in 1950, and as a consequence, cadmium levels in the air were reduced to below 0.5 mg/m^3 in most parts of the factory. By 1967, when a new platemaking department was built, the level of cadmium oxide dust in the air had been reduced to less than the threshold limit value (TLV) of 0.2 mg/m^3. From 1975 to the end of the study, the factory's levels of cadmium oxide dust were within the current TLV of 0.05 mg/m^3.

For the purposes of analysis, the author divided his cohort into 218 female employees, 1,066 male employees who were first employed before the amalgamation in 1947, and 1,494 males and 248 females who were first employed after the amalgamation.

Standard mortality ratios (SMRs) were computed. Expected deaths were generated on the assumption that the general population rates for England and Wales were operating in the study cohorts. Overall, the observed number of male deaths from all causes was slightly less than expected (observed = 591, SMR = 97). With respect to all forms of cancer, there was virtually no difference between observed and expected deaths (observed = 152, SMR = 100). On the other hand, a deficit of cancer deaths occurred to the subcohort of male employees who had been employed prior to the amalgamation (observed = 80, SMR = 84). But in males who were employed for the first time after the amalgamation, a significantly increased risk of total cancer deaths was apparent (observed = 72, SMR = 129, $p < 0.05$). This increased risk was partially attributable to an excess of lung cancer (observed = 32, SMR = 134, $0.05 < p < 0.10$) in the latter subcohort. In females, a slight nonsignificant risk of cancer was evident (observed = 22, SMR = 111). No detailed breakdown of female cancer mortality was provided by the author.

In both male subcohorts, those hired before 1947 and those hired after 1947, an excess but nonsignificant risk of cancer of the bronchus was evident (observed = 45, SMR = 114; observed = 32, SMR = 134, respectively). No significant excess risk of prostate cancer occurred in either group (observed = 4, expected = 4.1; observed = 3, expected = 1.9, respectively). Even after consideration was given to the time since first employed, no significant excess risk was seen in workers who were alive 15 years after first employment but who had left the company in any of the following cause-of-death categories: all causes, combined cancer, cancer of the bronchus, and cancer of the prostate.

Upon further subdividing the cohort according to "exposed" versus "nonexposed" status, the author reported no significant excess risk due to prostate cancer (observed = 1, expected = 0.7) or cancer of the bronchus (observed = 10, expected = 8.3) in the "exposed" subcohort. The numbers became rather small, however, and as a consequence, the power of this study to detect a significant risk is diminished.

When consideration is given to length of employment and latency together, i.e., males formerly employed at the factory for less than 1 year and from 1 to 14 years but followed for over 15 years since the onset of employment, again no significant excess risk of bronchial cancer or prostate cancer is apparent. No information was provided concerning mortality in those workers with more than 14 years of employment in a factory manufacturing nickel-cadmium batteries. The author concluded, on the basis of his analysis, that no evidence exists to suggest an increased risk of cancer mortality due to exposure to cadmium oxide dust.

Sorahan's analysis of latent effects included only terminated employees who were alive 15 years or longer after initial employment but who terminated before achieving 15 years employment. Person-years of individuals who were employed for more than 15 years with the company by the cut-off date were not enumerated. Only if the individual left employment with the company by the 15th year were his person-years counted. This arrangement has the effect of altering the expected deaths by the non-inclusion of person-years of individuals who were at risk of death but who were still alive and working after 15 years, as well as those who worked longer than 15 years but had terminated.

Although the study controlled for the healthy worker effect and problems with overlapping exposure and follow-up period, no comparison of persons who worked longer than 15 years and who were either working or terminated was provided. Additionally, 82 persons remain untraced with respect to their vital status, while 10 additional deaths were noted for which causes of death could not be found. The non-inclusion of the causes of death of the deceased members of this subgroup would tend to create a slight downward bias in the SMRs.

Furthermore, the tabular data presented classifies the cohort into two categories of exposure: "exposed" and "non-exposed," although in the "Population" section of the study, the author describes the jobs in the factories in terms of "high," "slight," and "minimal" exposure to cadmium. A clearer detailed description is needed of how the three latter categories were reconstituted as "exposed" and "non-exposed" for the purposes of presenting the findings in tabular form. The author's treatment of the subject suggests that some portion of the study population received little exposure to cadmium. Further, no urinary cadmium concentrations are given to substantiate exposure. If this is so, perhaps these individuals should have been excluded from the study group. A better definition of intensity of exposure should have been utilized to present the tabular findings. It might have been more informative to present the tabular findings in terms of "high, "slight," and minimally" exposed subgroups, as described by the author in the text.

Overall, this paper presents no evidence of an increased risk of prostate cancer in cadmium-exposed workers. However, since several problems exist concerning the structure of the study, the diminishing sensitivity of the study in relation to certain highly exposed subgroups, the questionable evidence of exposure in a large portion of the cohort, and the lack of comparisons among certain subgroups, the study cannot be said to provide conclusive evidence that cadmium is not carcinogenic. Although 14 of the 15 analyses presented show small, statistically insignificant excesses of lung cancer, it might be more appropriate to call the results inconclusively positive for lung cancer.

Inskip and Beral (1982)

Inskip and Beral (1982) conducted a cohort mortality study on residents of two small English villages, Shipham and Hutton, situated within seven miles of each other. Shipham is located in an area of substantial soil contamination by cadmium from the remains of a zinc mine that had operated on the site for nearly 400 years, until the middle of the nineteenth century. The village of Hutton was selected as a control. Investigations accomplished by the British Department of the Environment's Shipham Survey Committee revealed average garden soil cadmium levels ranging from 2 to 360 g/g in the area, while national levels rarely exceeded 2 g/g. Cadmium was believed to be absorbed in the diet mainly through the consumption of home-grown vegetables. According to a survey conducted by Thomas (1980), the dietary intake of cadmium in Shipham averaged 0.20 mg per week (range 0.04 to 1.08), while the national consumption averaged 0.14 mg per week (range 0.09 to 0.18).

Some 501 residents of Shipham and 410 residents of Hutton were entered into the cohort on September 29, 1939, and were followed until December 31, 1979, when SMRs were generated by cause of death. Data for both cohorts were compared with population statistics for England and Wales. Excess risks of mortality due to hypertensive and cerebrovascular disease and genitourinary disease were found in the Shipham residents. Cerebrovascular disease (observed = 65, SMR = 140, $p < 0.05$) was significantly high in residents of Shipham, especially females (observed = 44, SMR = 144, $p < 0.05$), and although the authors stated that a significant risk of genitourinary disease occurs only at $0.05 < p < 0.1$, recalculating the risk using the Poisson method gives a value of $p \leq 0.03$, for an SMR of 222 based on eight deaths, a statistically significant result that appears not to be due to chance alone.

Only two prostate cancer cases were observed in each village. Thus, SMRs were produced that do not differ significantly from those expected, although they were based on small numbers. With respect to lung cancer, no significant risks are evident, although the risk of lung cancer in females appears slightly elevated in both Shipham (observed = 4, SMR = 199) and Hutton (observed = 3, SMR = 181), based on small numbers.

The authors noted that overall mortality for these two rural communities is low compared to that of England and Wales, partially because of urban-rural confounding. They maintain that some evidence exists that cadmium influenced the "pattern of disease" in Shipham, specifically as regards kidney disease. On the other hand, the authors claim that the results do not support an association of cadmium and cancer or respiratory disease in cadmium-exposed persons. However, with respect to cause-specific cancer mortality, their data lack sensitivity because of diminishing power due to small numbers.

Another problem with this study, in addition to its low sensitivity is the lack of information concerning each person's actual exposure to cadmium. Although length of residence prior to 1939 could not be ascertained for individuals in the Shipham cohort, the authors were able to establish that all of the people studied in Shipham had lived there for at least 5 years. Furthermore, only 70% could be assigned to exposure categories based on the locations of their residences in areas of high or low cadmium content in the soils. Also, as the authors pointed out, the soil cadmium content, measured in 1974, may not accurately reflect exposures in 1939.

The greatest difficulty with this study, however, is in the knowledge that the average dietary consumption of cadmium in Shipham at 0.20 mg per week (range 0.04 to 1.08) was really not very different from the national average of 0.14 mg per week (range 0.09 to 0.18). The failure to find a detectable significant excess of cancer in Shipham residents may be due to a lack of sufficient dietary exposure to cadmium in Shipham residents. Furthermore, the presumption is that the cadmium was introduced through the gastrointestinal tract and not via the inhalation route, that the lung was not the target organ for cancer, and that therefore a significant excess of lung cancer would not be expected in this study. Hence, this paper should be judged inadequate with respect to the detection of a risk of lung or prostate cancer.

Andersson et al. (1982)

Andersson et al. (1982) updated the earlier Kjellstrom et al. (1979) study by enlarging his cohort to 548 men and 101 women and requiring that cohort members have had a minimum of one year of cadmium exposure between 1940 and 1980 at only one alkaline battery factory in Oskarshamn, Sweden. Exposure levels were as described in the earlier Kjellstrom study, except that more recent data indicated that cadmium levels in the air generally fell below 20 g/m^3, and that nickel levels were below 50 g/m^3. Indeed, exposure to nickel seems to have been more prevalent in this factory than exposure to cadmium. Periods of exposure for members of the cohort ranged from 1 year to 52 years, with a median of 10 years. Twenty-five percent of the cohort were exposed for better than 22 years. Expected deaths were derived from cause-, calendar year-, and age-specific national rates of the Central Bureau of Statistics from 1951 to 1980. A total of 118 of the males died before 1981; the analysis was limited to deaths prior to age 80 because of the unreliability of death certificate data after age 79. The authors noted 103 deaths versus 122.6 expected, a deficit that was more than likely due to the "healthy worker" effect, and was confined mainly to cardiovascular disease (46 observed, 57.3 expected). If the analysis is limited to workers with a minimum exposure of 15 years, again a deficit occurs (50 observed, 58.4 expected). However, a significant increase in mortality due to nephritis and nephrosis was noted (3 observed, 0.41 expected, $p < 0.05$). A nonsignificant increase in the risk of prostate cancer was evident (3 observed, 2.5 expected).

The authors concluded that a causal relationship probably exists between earlier heavy cadmium exposure and the risk of renal disease, as well as a possible causal relationship with obstructive lung disease. The authors felt that one case of nasopharyngeal cancer was possibily due to exposure to nickel hydroxide, which is believed to cause nasal sinus cancer in man.

With regard to prostate cancer, the authors felt that their data suggested an increased risk--a finding that agrees with the earlier study by Kjellstrom et al. (1979). Because of this study's lack of sensitivity, however, nothing can be concluded from it with respect to lung cancer risks. Furthermore, latency was not evaluated in these workers. Useful data might have resulted if the lung cancer risk could have been evaluated without the requirement of a lengthy exposure. Former employees who worked less than 15 years, and who died from lung cancer many years later, could not be counted in tabulations in which 15 years of exposure were required for inclusion. The presence of nickel also precludes any definitive statement about the risk of cancer in these workers. For the above reasons, this paper must be judged inadequate for use in evaluating the risks of prostate cancer or lung cancer due to cadmium.

Kjellstrom (1982)

Kjellstrom (1982), in an updated historic prospective study of a cadmium nickel-battery factory, reported on mortality patterns in a cohort of 619 male employees (including 269 from an earlier study). During the study period from 1951 to 1980, 103 workers died, as compared to 126.4 expected on the basis of Swedish mortality statistics. The highest SMR was for urogenital disease, with 4 observed deaths versus 2.5 expected. This SMR is considered to be nonsignificant. Only 4 prostate cancer deaths occurred, versus 3.1 expected. The workers in this study cohort had a minimum of one year's exposure to cadmium.

The author noted that, based on preliminary data, prostate cancer mortality was "more increased than the mortality due to other causes." This increase was not statistically significant, however.

The average historic exposure levels within this plant are depicted in Figure 1. From 1946 to 1976, there appears to have been a 1,000-fold drop in average exposure levels. A detailed analysis of past and present cadmium exposures in this factory has been published (Adamsson, 1979). The author reports that nickel exposure levels have been at least the same as that of cadmium, and often as much as 10 times higher.

This study presents a number of problems. The records of employees terminated prior to 1945, a group in which the greatest risk is likely to be found, are nonexistent. Almost 31% of this group had exposures to cadmium of less than 2 years' duration. Almost 50% of the cohort (301 workers) received their first exposures to cadmium after 1959, which means that a large proportion of the cohort had not been followed even for 20 years, and thus, not enough time had elapsed for reliable evaluation of cancer risks. Furthermore, smoking information was not available for the older workers, a subgroup in which the greatest cancer risk is likely to be found. This may have been the reason why no results evaluating the effects of smoking were presented in the study, although a detailed data base was reported by the author to be in the development stages as an extension of the study for future follow-ups. Additionally, the author reported that for cancer of the prostate, the rate ratio increased with increasing latency and increasing dose. He reported rate ratios of 1.27, 1.33, and 1.55, corresponding to the exposure categories of > 0 years, > 1 year, and > 5 years. In the > 1 year exposure duration category, prostate mortality rate ratios of 1.33, 1.44, and 1.81, corresponding to latency periods of 1, 10, and 20 years, respectively, were given. However, since no tabular

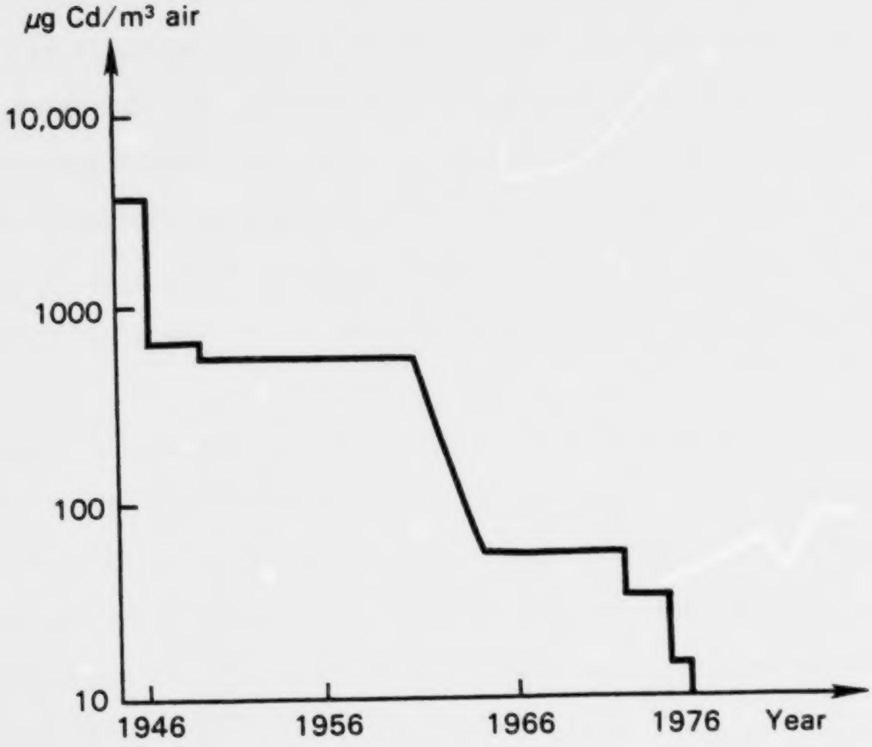

Figure 1. Concentration of cadmium in the air (μg Cd/m^3) from 1949 to 1976. Arithmetic mean of stationary and personal samples.

SOURCE: Kjellstrom, 1982.

data were presented, it is not possible to determine how the four observed prostate cancer deaths were distributed into the subcategories referred to by the author. The author did note that the numbers were too small for the detection of statistically significant differences.

Kjellstrom repeated the analysis for urogenital diseases. For those with more than 20 years' exposure and 20 years' latency, 4 observed urogenital deaths occurred versus 0.93 expected ($p < 0.05$). This type of disease was found exclusively in the form of nephritis of the kidney. Again, it is difficult to conclude without evaluation that cadmium exposure was implicated, although the author himself stated that it is "clear that cadmium exposure increases mortality from kidney diseases" after high exposure intensity and long duration of exposure. The author noted a tendency in his data for a slightly increased nonsignificant risk of prostate cancer from exposure to cadmium.

In addition to the main study discussed above, Kjellstrom (1982) included discussions of three Japanese studies (Japan Public Health Association [JPHA], 1979, also reported by Shigematsu et al., 1981; Nogawa et al., 1978; and Nogawa et al., 1981) and a description of another ecological study planned by himself and the Department of Epidemiology at the University of Tokyo, for which only preliminary findings are available. In this latter study, age-standardized death rates in cadmium-polluted areas for persons 35-84 years of age were compared with the respective rates in non-cadmium-polluted areas. Preliminary data, according to Kjellstrom, suggested a nonsignificant tendency toward higher mortality rates in cadmium-exposed areas as compared with control areas (an age-adjusted mortality rate of 176 per 1,000 in cadmium-exposed areas versus 139 in the control areas). Prostate cancer and kidney disease mortality rates were also higher in the cadmium-exposed areas, but most of the prostate cancer mortality excess occurred in individuals 85 and over. No tests of significance were done. This analysis was reported by Kjellstrom as tending to support the hypothesis of a cadmium effect, but "definite conclusions have to be left until all the analyses are completed."

Of the Japanese studies referred to by Kjellstrom (1982), the first (JPHA, 1979, also reported by Shigematsu et al., 1981) was an analysis of cadmium exposure and mortality in the general environment. According to the author, people in many areas of Japan endure high cadmium exposures of up to several micrograms per day from consumption of contaminated rice. For each of four prefectures of Japan, age-standardized mortality rates were calculated in a cadmium-exposed area and compared to those calculated in a nonexposed reference area of the same prefecture. It was found that cancer mortality rates were generally about the same in the nonpolluted areas as in the polluted areas, but no significance tests were done. The only diseases for which death rates were found to be lower in the non-cadmium-polluted areas were kidney diseases and diabetes. With respect to prostate cancer mortality, two of the polluted areas had higher death rates than did the controls, while in two others the reverse was true. The author noted that the two prefectures with higher death rates of prostate cancer were the areas with the "highest likely cadmium exposure to the population." The former two prefectures tended to have higher rates of mortality from kidney disease and hyperplasia of the prostate as well. Because this was an ecological study, it can only be considered as suggestive of areas for future research.

The second Japanese study (Nogawa et al., 1978) found that in 2,689 men and women over age 50, the village-specific prevalence of low molecular weight proteinuria (LMWP) increased with an increase in the village-specific average cadmium concentration in rice. LMWP was measured by urinary retinol binding protein. It is very likely that this ecological study included persons who had never been exposed to cadmium in rice, as well as persons with prior-existing conditions, possibly introduced long before they were exposed to relatively high concentrations of cadmium in rice. The positive association noted by the author should not be construed to signify a causal association.

In the third study, Nogawa et al. (1981) conducted a mortality study of the 81 men and 124 women identified in the earlier study as having LMWP. They, along with the remaining men and women not found to have LMWP, were followed from 1974 to 1979. The authors found a significant ($p < 0.05$) twofold excess risk of death for men with LMWP and a nonsignificant 1.2-fold excess risk of death for women with LMWP. Mortality rates were based on 27 deaths of males with LMWP and 30 deaths of females with LMWP. A positive association of LMWP with heart disease, cerebrovascular disease, nephritis, and nephrosis was noted. This association raises the specter of a possible confounding effect of hypertension with LMWP. If hypertension is a cause of LMWP, the higher mortality of the individuals that had LMWP may have been due to hypertension and not, as the author suggested, to cadmium exposure. The correlation with LMWP may thus be spurious, and hence, conclusions drawn from this study regarding an association of higher mortality with cadmium exposure must be characterized as certainly no more than suggestive.

Armstrong and Kazantzis (1983, 1982)

Armstrong and Kazantzis (1983) recently completed a cohort mortality study of 6,995 male cadmium workers born before 1940, who had had at least one year of employment during 1942-1970 in one of five British industries (primary production 64%; copper-cadmium alloy 8%; silver-cadmium alloy 14%; pigments and oxides 8%; and stabilizers 6%). The authors classified their cohort (derived from 17 major plants) into the following three categories of exposure: 1) "always low" (80%; 5,623 workers); 2) "ever medium" (17%; 1,173 workers); and 3) "ever high" (3%; 199 workers). Expected deaths were derived from SMRs based on mortality rates for the population of England and Wales. In addition, the authors referred to "approximately accounting" for regional variations in mortality by the use of cause-specific SMRs for standard regions published by the British Office of Population Censuses and Surveys during the period 1969-1973. This procedure is not completely described. The authors stated that in one instance they used the urban aggregate of a primarily rural region to derive SMRs for a plant that was situated in an urban portion of the region. The authors developed two-sided confidence intervals for significance testing through the use of the "exact" Poisson distribution method for some comparisons and the "normal" distribution for others.

These authors developed job categories that reflect the categories of intensity of exposure ("ever high," "ever medium," and "always low") based in part on expected cadmium urine concentrations. The authors' classification scheme is described as follows in their detailed report of April, 1982 to the International Lead Zinc Research Organization:

> The classification of a job was based on an assessment of the absorption of cadmium by those working in that job, as indicated by concentrations of cadmium in urine, where these were available. "High" jobs entailed exposures which were judged likely in the long term to lead to cadmium urine concentrations of over 20 μg/l. This category was assigned only to certain jobs in the past, when conditions were often very much worse than any pertaining today. Workers exposed for long periods in these jobs have shown levels of cadmium in urine as high as 100 μg/l or more. "Medium" jobs entailed mean exposure less than "High" jobs, but would lead to cadmium in urine concentrations sufficiently elevated for these to be clearly distinguishable from an occupationally unexposed group, even by the methods of evaluation of urinary cadmium which were available in the 1960s. An appreciable number of cadmium in urine concentrations over 5 μg/l would be expected in a group of workers with long term service in a "Medium" job. The remaining jobs

> are classified as "Low." Such jobs would involve some occupational exposure to cadmium, but at concentrations too low to meet the criterion for inclusion in the "Medium" category.

In the author's "ever high" exposed group, only 3%, or 199 members of their cohort, qualified (a minimum of at least one year spent in a high-exposure job) (see Table 16).

Approximately 96% of this cohort was classified with a known vital status, whereas 4% either emigrated or were not traced. The authors excluded 38 deaths occurring to individuals 85 years of age or over. Presumably the authors ceased counting person-years for those live individuals who reached age 85 and over as well in order to retain comparability. The SMR for all causes of death was 97 (based on 1,902 deaths). The SMR for the first 10 years of follow-up was 79 (based on 205 observed deaths) and for later years was 99 (based on 1,697 deaths), a phenomenon due most likely to the healthy worker effect. The authors found a significant excess of mortality due to bronchitis in the "ever high" exposure group, which appears to be dose-related (12 observed vs. 2.8 expected, $p < 0.01$) without regard for latency. This risk diminishes to a nonsignificant SMR of 138 in the "ever medium" group and finally to an SMR of 121 in the "always low" group, without regard for latent factors. Prostate cancer remained nonsignificant in all three exposure categories, without regard for latent factors. Because of the small numbers involved, however, the study could not detect a prostate cancer risk in the "ever high" exposure category. Although the authors stated that this cohort had been analyzed according to years since time of initial exposure, in the published version only the overall SMR was presented for those with 10 years or more of follow-up. Also, no detailed tabular data were provided with respect to lung cancer or prostate cancer by time since onset of initial employment in the published results.

TABLE 16. PERCENT DISTRIBUTION OF STUDY POPULATION BY LEVEL OF INTENSITY OF EXPOSURE

Intensity of exposure[a]	Urine cadmium concentration[a]	Armstrong et al. (1983)
Always low	< 5 μg/L	80%
Ever medium	5 - 20 μg/L	17%
Ever high	> 20 μg/L	3%
Cohort size	--	6,995

[a] Definition from Armstrong and Kazantzis, 1982.

The authors agreed that the number of persons in the "ever high" exposure group (N = 199) was too small to preclude the possibility of the existence of a risk of prostate cancer from exposure to cadmium in this group. They further noted that no cases of prostate cancer turned up in the "ever medium" group, whereas 2.5 were expected. Prostate cancer was near to expected levels in the "always low" exposure group (23 observed, 20.4 expected) into which the large majority of the cohort fell. However, the authors provide no breakdown of site-specific cancer by time (10, 15, or 20 years) since onset of initial employment according to their three categories of exposure. Of interest is whether sufficient power remains in the study to detect a significant excess risk of prostate cancer in the latter two categories of exposure, particularly the "ever medium" group, 10, 15, or 20 years after the onset of exposure.

Furthermore, the possibility exists that when workers of 17 different plants are thrown together to form a massive cohort for study, some of these workers may have had little or no exposure to cadmium. If this occurred in the study under discussion, the likelihood of detecting a risk is reduced by the inclusion of person-years for individuals who essentially were not exposed to cadmium. This is especially true if there is a dose-response relationship operating in the cohort. Unless reliable criteria are established to quantify individual exposures to cadmium dust and compounds of cadmium, in addition to other confounding substances that may be present, it cannot be presumed that every member of this cohort was exposed to cadmium in high enough quantities to produce a detectable health risk. Furthermore, although some recent monitoring data may exist with which to quantify exposures, it is questionable that sufficient industrial exposure measurement data exist from the 1940s or 1950s and earlier to provide more than a guess at the levels of exposure to cadmium and other metals that existed when these persons were first employed. It may be that the historical prospective study design is not a sensitive enough analytical tool to be used in assessing cancer risks in a cohort of workers who, in general, were exposed to only "low" levels of cadmium. On the basis of the above factors, this study is seen to provide no evidence that cadmium is a powerful prostate carcinogen.

On the other hand, although the risk of lung cancer overall was not significant (observed = 199, SMR = 107) without regard to intensity of exposure, the subgroup of workers who were employed for 10 or more years in low-exposure jobs exhibited a statistically significant excess risk of lung cancer (SMR = 126, observed = 100, $p < 0.05$) (Table 17). The authors, in an earlier draft of this paper (Armstrong and Kazantzis, 1982), presented data concerning the lung cancer risk in workers having a minimum of 10 years' employment in the categories of "ever high" and "ever medium" exposure to cadmium. With respect to the "ever high" exposure category, no evidence exists of an elevated risk of lung cancer (SMR = 87*, observed = 2) after 10 years' employment; however, little power remains with which to detect an elevated risk in that group. The power to detect a twofold excess of lung cancer in this category is only 0.11, and for a threefold risk it is 0.30. On the other hand, a suggestion of an elevated risk is apparent in the "ever medium" exposure group (SMR = 142, observed = 16) with 10 or more years of employment in the industry. It would have been valuable, however, to include a discussion of the lung cancer risk by longer time intervals since onset of exposure (i.e., 15 or 20 years). Power considerations probably would render such calculations of lung cancer risk in the "high" exposure subcohort and the "medium" exposure subcohort questionable.

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*Due to an error in the authors' calculations, this SMR was given as 87 when it should have been 83.

TABLE 17. LUNG CANCER SMRs BY EXPOSURE GROUP FOR MEN WITH TEN OR MORE YEARS OF EXPOSURE

Exposure level	Observed	Expected	SMR	(95% CI)
Always low	100	79.1	126[a]	(102-151)
Ever medium	16	11.3	142	(81-230)
Ever high	2	2.4	83	(10-301)
Total	118	93.2	127[a]	(104-150)

[a] Significant.

SOURCE: Kazantzis, letter of February 10, 1984.

The increased risk of lung cancer in the "always low" exposure category cannot be ascribed necessarily to cadmium exposure. It is generally accepted that manual workers smoke more than the general population; thus, it is not inconceivable that some of this increased risk is due to smoking. The authors state further that the absence of a gradient of risk with intensity of exposure makes it unlikely that the excess is due to cadmium. A full tabulation of SMRs in the three exposure intensity categories by time since onset of exposure (10, 15, and 20 years) and similar duration of employment intervals might provide better dose-response information.

The exceptionally high risk of bronchitis in the "ever high" exposure group cannot be attributed to a cigarette smoking link because of the lack of a social-class gradient in the three exposure intensity categories. Although it is possible that other industrial pollutants may have contributed to this excess in the "ever high" exposure group, the authors point out that the size of the excess is much too great to be solely attributable to such confounding effects. Hence, they conclude that cadmium may have contributed to the excess of bronchitis.

Overall, this study did not sufficiently address the impact of latency and duration of exposure on the risk of prostate cancer, lung cancer, and hypertensive disease, i.e., because it considered only a single cut-off point (10 years). Perhaps additional tabulations that the authors state are in their possession can provide answers to the questions raised. While this study provides no evidence of a risk of prostate cancer, the possibility remains that at the exposure intensities indicated following a lapse of 10, 15, or 20 years from initial exposure, the historic prospective method may no longer be sensitive enough to detect a prostate cancer risk, if in fact one exists.

Based on the authors' definition of exposure, only 3% (or 199 employees) could have been expected to have achieved a urine concentration of 20 g/L cadmium, as contrasted with 100% (or 602 employees) of the Thun et al. (1985) cohort. It appears that there is an absence of evidence of exposure to concentrations of cadmium that would produce a detectable cancer effect in this cohort. Eighty-one percent of this cohort fell into the exposure category

"Always low," i.e., < 5 g/L cadmium urine concentration, considerably less than the exposures sustained by the Thun et al. (1985) cohort. The vast majority of the Armstrong and Kazantzis cohort consisted of members who had had very little exposure to cadmium.

A significant excess risk of lung cancer appears evident in workers with 10 years of "low" exposure to cadmium; however, this excess risk is not necessarily due to exposure to cadmium. Comparable data in the "ever medium" exposure group indicates a nonsignificant risk of lung cancer, but latency is not evaluated in sufficient detail. Perhaps further follow-up might sharpen the excess found in this category. The data from the "ever high" group lack sufficient sensitivity to be judged adequate for the detection of a risk of lung cancer. It would be of interest to see if the addition of the 38 causes of death of persons over age 85 would alter the calculated risks. It might also be of some value to repeat the analysis on a plant-by-plant basis to determine which plants exhibit the highest risks by cause, and then develop exposure indices for those plants.

Nothing can be said on the basis of this study concerning the risk of hypertensive disease, except that it bears watching. However, the risk of bronchitis, which the authors conclude is probably due to exposure to cadmium dust, appears to be very significant. The dose-response relationship noted by the authors for bronchitis cannot entirely be attributed to confounding effects.

Sorahan and Waterhouse (1983)

Sorahan and Waterhouse (1983), in an update of the earlier study by Sorahan (1981), employed a technique referred to as the "method of regression models in life tables (RMLT)" by Cox (1972) and Kneale et al. (1981) to test the null hypothesis that occupational exposure to cadmium is not associated with excess mortality. Only one set of mortality data was derived by means of calculating SMRs. Without qualification, only the risk of respiratory cancer was found to be statistically significant (observed = 89, expected = 70.2, $p < 0.05$). The risk of prostate cancer was elevated slightly but not significantly (observed = 8, expected = 6.6) in this phase of the study. These data, however, may not include one to four of the earlier prostate cancer cases found by Kipling and Waterhouse (1967), for the reasons stated below.

In the second part of their study, utilizing the RMLT, the authors prepared analyses with and without the four original cases included. The authors believed that only new cases of prostate cancer should be used to determine an RMLT-derived asymptotically normally distributed test-statistic measuring the significance of cancer of the prostate in their cohort. The potential confounders of sex, hiring date, age at hire, length of employment, and employment status were controlled for by stratifying the data into sub-groups defined by all possible combinations of various levels of these controlling variables. Exposure was defined to be cumulative duration of employment in a "high" exposure job, and secondly as cumulative duration of employment in a "high or moderate" exposure job. Job categories were classified by exposure to cadmium as "high exposure," "moderate (or slight) exposure," and "minimal exposure." Only 8 jobs were considered to involve "high" exposure, while 14 were considered to involve "moderate (or slight)" exposure, and 53 were considered to involve "minimal exposure." With the four original cases included, the test-statistic (3.10, $p < 0.05$) was significant for the variable "highly exposed," but was nonsignificant (-0.32) when the original four cases were excluded. Even when reduction in exposure levels over calendar year periods was programmed into the analysis (assumed exposure levels from 1968 to 1972 were 40%

of levels existing prior to 1967, and 10% post-1972) the test-statistic increased to 3.52 ($p < 0.01$) with the original four prostate cancers included. The authors, however, chose to note instead that "the effect of excluding the four previously reported cases of prostatic cancer is to reduce the statistically significant positive statistic to a small nonsignificant negative statistic." They concluded that "no new evidence has been produced which suggests an association between occupational exposure to cadmium and cancer of the prostate." If these persons are to be excluded, such exclusion should be accomplished by redefining the study cohort so that selection biases do not creep into the results. This could perhaps be accomplished by defining a later time of initial employment.

The test-statistic generated for respiratory cancer in the "high-exposure" category in men is nonsignificant at 1.28, but for "high to moderately exposed" individuals, it is significant at 2.51 ($p < 0.05$). The authors suggested that exposures to the welding fumes of oxyacetylene found in jobs of "moderately exposed" workers might have accounted for this excess, which was chiefly confined to workers who began employment prior to 1940 (3.09, $p < 0.05$), to those who worked a minimum of 6 years (2.49, $p < 0.05$) and to those observed for 30 years or longer (3.18, $p < 0.05$). A significant test-statistic (2.36, $p < 0.05$) was also obtained for a third exposure estimate (duration of "high" or "moderate" exposure employment, excluding welding) for the period 30+ years after first employment. In no instance did age, sex, year of starting employment, or years of follow-up produce a significant test-statistic for lung cancer in the group with the highest potential exposure to cadmium.

The authors pointed out the possibility that since job applicants with histories of lung and kidney disease were traditionally excluded from "high-exposure" jobs, this would tend to work against the demonstration of a potential hazard for related diseases in this category. They also indicated that since only 12% of their 599 deaths were in workers with more than 5 years' high-exposure employment, but 24% were in workers with moderate- or high-exposure employment of more than 5 years, this might explain why a significant statistic was not found for lung cancer in the "high" exposure group if, in fact, occupational exposure to cadmium oxide is a risk factor. Presumably, this differential mortality may indicate a lack of sensitivity in the "highly" exposed group due to small numbers. If such a risk dose not exist in truth, the explanation for the seemingly inverse dose-response effect may be due to exposure to oxyacetylene welding fumes, exposure to nickel hydroxide dust, or to chance alone.

The authors felt also that although information on their cohort's smoking habits was not available, if smoking were the reason for an excess of respiratory cancer, then similar associations should be expected for diseases of the circulatory system, and such associations were not found. The authors stated that the analysis could not differentiate between exposure to cadmium oxide dust and exposure to nickel hydroxide because almost every job with high cadmium exposure also had high nickel exposure.

In conclusion, Sorahan and Waterhouse (1983) found an increased risk of prostate cancer that was entirely dependent on the original four cases of Kipling and Waterhouse (1967), but found no association with prostate cancer for cases subsequent to these. They also found an increased risk of respiratory cancer among workers moderately or highly exposed to cadmium oxide dust and initially employed before 1940--a finding which was confounded by exposures to oxyacetylene welding fumes and to nickel hydroxide dust.

Varner (1983, unpublished)

ASARCO Inc., the owners of the cadmium processing plant that had been studied by Lemen et al. (1976), updated that study with one of their own (Varner, 1983, unpublished) in which all employees were included who had had at least six months of employment at the cadmium processing plant between January 1, 1940 and December 31, 1969. The size of the cohort was enlarged to 644. This preliminary report was accompanied by a letter to David Bayliss of the CAG from Lowell White of ASARCO, dated January 11, 1984, in which White indicated that the follow-up for this study extended to the end of 1981.

Varner (1983) used a methodological technique called the Standardized Cause Ratio (SCR), which is analogous to the calculation of proportionate mortality ratios. Expected deaths for particular causes of death are derived by dividing age- and cause-specific attributable deaths by total deaths in the age and year category corresponding to each particular decedent's age and year of death. The resulting proportions are summed to arrive at the number of expected deaths. Their analysis was reported at the time to be under peer review, according to White (letter to David Bayliss, CAG, January 11, 1984).

The preliminary findings of Varner (1983) differed from the Lemen et al. (1976) study in that the risk of prostate cancer was found to be no longer statistically significant, although it was still elevated (observed = 5, SCR = 169)*, while the risk of lung cancer remained statistically significant (observed = 23, SCR = 163). The author attributed the excess risk of lung cancer in his study to several factors: increased cumulative exposure to cadmium, years of exposure, age at death, latent period, and/or cigarette smoking.

The author maintains that a "substantially higher than normal prevalence of heavy cigarette smoking" in a subcohort of the main study cohort may have contributed to "part or all" of the increased lung cancer incidence. Other findings include a significant risk of urinary tract cancer (observed = 6, SCR = 252, $p < 0.05$); specific bladder cancers (observed = 5, SCR = 374, $p < 0.01$);

total cancer (observed = 53, SCR = 126, $p < 0.05$); nonmalignant respiratory disease (observed = 7, SCR = 153, $p < 0.05$); ulcer of the stomach and duodenum (observed = 7, SCR = 452, $p < 0.01$); and accidents (observed = 19, SCR = 150; $p < 0.05$). However, the findings also reflect a significant deficit of deaths due to heart disease (observed = 68, SCR = 77, $p < 0.01$) and stroke (observed = 6, SCR = 40, $p < 0.05$).

Calculated cumulative exposure to cadmium (mg-years/m^3) was determined for every member of the cohort on the basis of personal monitoring measurements made during the period 1973-1976. The author pointed out that this variable assumes that exposures over several decades were about the same. The author felt that such a procedure tends to underestimate exposures of many years ago when cadmium levels were probably higher, while at the same time tending to overestimate exposures of recent years.

Varner (1983) found that a dose-response relationship existed with respect to lung cancer, and to a lesser degree, total malignant neoplasms, as follows:

Exposure (mg-years/m^3)	Lung cancer		Malignant neoplasms	
	Observed	SCR	Observed	SCR
0-4	7	95	23	108
5-15	6	159	14	123
16+	10	332 ($p < 0.01$)	16	168

Lung cancer was also found to be related to smoking in the following manner:

Pack-years	Observed	SCR
Unknown	10	115
Nonsmokers	0	---
1-19	2	183
19	11	313 ($p < 0.01$)

No such effects were seen for bladder cancer.

With respect to lung cancer, the author reports that 77.5% of the cadmium workers had been smokers, and that 53.2% had achieved 20 or more pack years. Varner, citing statistics from a 1970 Household Interview Survey by the National Center for Health Statistics, reported that 69.2% of blue collar workers had ever smoked, and that 28% had smoked a pack or more of cigarettes a day at some time in their lives. Thus, Varner concluded that evidence exists for a potential confounding effect due to cigarette smoking, since the proportion of smokers in the Varner (1983) cohort appears to be somewhat greater than that shown by survey data.

In the letter attached to this preliminary paper, Dr. White cautioned that several problems had to be solved concerning the validity of the study's findings, not the least of which involved the credibility of the derivation of SCRs. The National Institute for Occupational Safety and Health (NIOSH) update of the Lemen et al. (1976) study, which is reviewed later in this section, also contained 60 fewer individuals, who were allegedly excluded by NIOSH for "various reasons" upon which Varner does not elaborate. Varner claimed that he included all individuals "regardless of exposure." However, Dr. Michael Thun of NIOSH, in an internal memorandum, a copy of which was given to the Carcinogen Assessment Group (CAG), states that the eligibility requirement for inclusion of workers into the study cohort was decided on, in advance, by NIOSH and ASARCO, and that both Varner and Lowell White were aware of it (memorandum, October 17, 1984). Therefore, Dr. Thun maintains, NIOSH was not inconsistent in adhering to the eligibility criteria, contrary to the letter from White. NIOSH removed 10 persons from the cohort because they were either non-white or female; hence, only 602 males were included in the NIOSH study by Dr. Thun.

Another problem with the study is that the death certificates were received only 2 weeks prior to the presentation of the paper at the Fourth International Cadmium Conference, thus necessitating the use of cause-of-death codes that appeared on the death certificates as they were received. Both the NIOSH cause-of-death codes and those of the state are described as differing. White referred to the presence of what he termed "nosology bias" in the ascertainment of underlying causes of death. He stated that some 93 death certificates were coded by a different nosologist than the one who performed the coding for the preliminary report, leading to 21 distinctly different cause of death codes. The authors are seeking a neutral "unbiased" method for coding death certificates prior to the issuance of a final report on the study. Furthermore, White believes that the possible presence of confounding variables as an explanation for elevated risks, especially of lung cancer, has not been properly or completely addressed in this preliminary report. White reported that Michael Thun and his coworkers at NIOSH (Thun et al., 1985) attempted to account for the contribution of arsenic exposure and cigarette smoking in their study, which is reviewed herein. Additionally, White reported that the follow-up through 1981 was incomplete, although the percentage remaining with an unknown vital status was not given. He reported that ASARCO recently contracted with the Social Security Administration to provide vital status information, and that the "final procurement" of death certificates for the study was expected to begin soon after the date of his letter (January 11, 1984). The cohort has been expanded, and a number of newly found personnel records have been included for evaluation in the final report.

Because of the very preliminary nature of the Varner (1983) study in its present form, the results will not be prejudged here. Although the author found a dose-related significant excess risk of lung cancer, as he explains, this may be due in part to the confounding effects of smoking and/or arsenic exposure. Additionally, although the risk of prostate cancer is elevated, it is no longer statistically significant. Whether the final version of the study will sustain such a finding is not presently clear, in view of the many problems that must be solved. It does not appear at this time that the final version of the study will be forthcoming in the very near future.

Hence, the Varner study cannot, at present, be used either to substantiate an excess risk of lung cancer due to cadmium exposure or to refute the earlier findings of significant prostate cancer in the Lemen et al. study.

Thun et al. (1985)

In an enlargement and update of the Lemen et al. (1976) study, Thun et al. (1985) broadened the cohort to include 602 white males who had worked a minimum of 6 months in production work during the period 1940-1969. The resulting cohort was followed an additional 5 years to the end of 1978. The difference between the size of the Varner (1983) cohort of 644-602 = 42 and the Thun et al. (1985) cohort was described by Thun as being due to the inclusion of 32 persons who had worked less than one year and 10 non-whites and females in the Varner cohort (memorandum, August 17, 1984). Cause-specific mortality rates for seven causes of death, suspected *a priori* of being related to cadmium exposure, were compared between the cohort and U.S. white males. Death certificates were coded by a qualified nosologist according to the protocol of the version of the International Classification of Diseases (ICD) in effect at the time of death. Expected deaths were calculated using the life-table system developed by NIOSH. The risk of lung cancer (observed = 20, SMR = 265, $p < 0.05$) was significantly in excess among workers hired both before and after the cessation of arsenic smelting in 1925 and having been employed for 2 or more years (Table 18). Prostate cancer was no longer excessive in these workers.

TABLE 18. MORTALITY FROM LUNG CANCER (ICD 162-163)
BY DATE OF HIRE, WITH MALE CADMIUM PRODUCTION WORKERS

	Observed	Expected	SMR	95% confidence interval
Hired prior to 1/1/26	4	0.56	714	195-1,829
Hired on or after 1/1/26	16	10.87	147	84-239
Overall cohort ≥ 2 years employment	16	7.00	229	131-371
Total ≥ 2 years employment	20	7.56	265	

SOURCE: Thun et al., 1985.

From the data given in Table 19, it was estimated that inhaled exposure concentrations decreased with the introduction of a mandatory respirator program in the early 1940s and ventilation controls in about 1970. The estimates are based on personal work history area monitoring data, adjusted to reflect actual inhaled exposures during the wearing of respirators. The source of the data--the plant's personnel records--provided enough detail so that broad job categories could be assigned to each period of a worker's employment.

The plant studied has produced cadmium metals and cadmium compounds from 1925 to the present. It was an arsenic smelter from 1918 to the early 1920s, when it was shut down for several years, and was a lead smelter from 1886 to 1918. Urine cadmium data, which were available for 261 members of the cohort employed beyond 1960, suggested a highly exposed population. Since arsenic

TABLE 19. ESTIMATES OF INHALATION EXPOSURES (mg/m^3) BY PLANT DEPARTMENT AND TIME PERIOD[a]

Time Period	Sampling	Roaster	Mixing	Calcine	Solution	Tankhouse[b]	Foundry	Retort	Pigment	Office and Lab[c]
Pre-1950	1.0	1.0	1.5	1.5	0.8	0.04	0.8	1.5	0.2	0.02
1950-1954	0.6	0.6	0.4	1.5	0.8	0.04	0.1	0.2	0.2	0.01
1955-1959	0.6	0.6	0.4	1.5	0.4	0.04	0.1	0.2	0.04	0.01
1960-1964	0.6	0.6	0.4	0.4	0.4	0.02	0.1	0.2	0.04	0.007
1965-1976	0.6	0.6	0.4	0.15	0.04	0.02	0.04	0.2	0.04	0.007

[a] Estimated inhalation exposures occurred in various departments and were based on area monitoring data adjusted to reflect the actual exposures of workers wearing respirators.

[b] Tankhouse estimates were also used for non-production plant departments (e.g., repair shops) that were not measured directly.

[c] Office estimates were also used for non-plant areas (e.g., the plant guard) that were not measured directly.

SOURCE: Smith et al., 1980.

is a known lung carcinogen, the authors separated arsenic-exposed workers from the rest of the cohort by dividing their cohort into two subgroups, those employed on or before January 1, 1926, and those employed after that date.

In the first group, 4 lung cancer deaths were observed versus 0.56 expected, while in those employed 2 years or longer after January 1, 1926, 16 observed lung cancer deaths were observed versus 6.99 expected, $p < 0.05$ (Table 18).

A dose-response relationship was also observed between lung cancer mortality and cumulative exposure to cadmium (Table 20). At a cumulative exposure of less than 584 mg-days/m^3, both the SMR and the SRR are less than expected at 53 and 0.48, respectively. As cumulative exposure increases to between 584 and 2,920 mg-days/m^3, the SMR and SRR increase to 152 and 1.55, respectively. Finally, at cumulative exposures above 2,921 mg-days/m^3, the SMR and SRR increase significantly to 280 and 3.45, respectively. Cumulative exposure to cadmium was calculated based upon length of employment and jobs within the plant. Average exposure to airborne cadmium was calculated based on the industrial hygiene data in Table 19. Each worker's cumulative exposure over time was the sum of the products of number of days worked in each given job category by the average inhalation exposure of each job category during each respective time period throughout the entire period of employment of that individual.

With respect to arsenic exposure after 1925, a small and unspecified number of workers processed arsenic intermittently in one building of the complex. This lasted into the 1930s. A second, continuing source of arsenic exposure came in the sampling, mixing, roasting, and calcine furnace areas. Six industrial hygiene measurements in 1950 showed arsenic concentrations

TABLE 20. LUNG CANCER (ICD 162-163) MORTALITY BY CUMULATIVE EXPOSURE TO CADMIUM: WHITE MALES HIRED ON OR AFTER JANUARY 1, 1926

Cumulative exposure (mg-days/m^3)	Forty-year TWA equivalent[a]	Deaths	SMR[b]	SRR[c]
$\leq$ 584	$\leq$ 40 μg/m^3	2	53	0.48
585-2,920	41-200 μg/m^3	7	152	1.55
$\geq$ 2,921	> 200 μg/m^3	7	280[d]	3.45
	U.S. white males	-	100	1.00

[a] Represents the time-weighted average (TWA) that, over a 40-year working lifetime, would result in this cumulative exposure.

[b] SMR = Indirectly standardized mortality ratio.

[c] SRR = Directly standardized rate ratio, relative to the U.S. white male general population.

[d] $p < 0.05$.

SOURCE: Thun et al., 1985.

ranging from 300 to 700 $\mu g/m^3$ in the vicinity of the roasting and calcine furnaces, the highest measurement anywhere in the plant. The authors report that later measurements by the company and the U.S. Occupational Safety and Health Administration (OSHA), in 1979, indicated a decrease in arsenic concentration to around 100 $\mu g/m^3$ in this area. However, the author points out that although air levels of arsenic in this specified area were 10 times the OSHA threshold of 10 $\mu g/m^3$, the personal exposures of individuals in this area were lower because of respirator usage--a practice that had been in effect since the 1930s (Smith et al., 1980). In fact, on the basis of the assumption that workers received more exposure to arsenic then they really did, the authors estimate that the average arsenic exposure of persons in this study would have been no more than 25 $\mu g/m^3$ under the following conditions:

(1) assuming the average airborne arsenic exposure was 500 $\mu g/m^3$ in the high-arsenic work areas (i.e., calcine furnace, mixing, roasting, and sampling);

(2) assuming a respiratory protection factor of 75%; and

(3) estimating that 20% of the person-years of exposure were spent in high-arsenic work areas (based on personnel and biological monitoring data).

Hence, according to the authors, if the 586 workers hired after 1926 were employed for an average of 3 years, they would have acquired 1,758 person-years of exposure to 25 $\mu g/m^3$ of arsenic. Based on an OSHA risk assessment model for arsenic (OSHA, 1983), such an exposure should have resulted in no more than 0.78 lung cancers. The authors feel that the 25 $\mu g/m^3$ figure overestimates actual exposures because only a fraction of jobs in the "high-arsenic" areas involved exposures as high as those in the furnace areas.

High-exposure jobs in the roaster area were frequently staffed by entry-level workers with less than 6 months' employment, who would for that reason never qualify for inclusion in the study, although the authors included them in their estimate that 20% of the person-years of exposure were in "high-arsenic" jobs. Furthermore, the authors point out that urinary arsenic levels from 1960 to 1980 averaged 46 μg/L, which is consistent with an inhaled arsenic concentration of 14 $\mu g/m^3$. Therefore, if one assumes an average inhaled concentration of 125 $\mu g/m^3$ (25% of 500 $\mu g/m^3$) over 3 years, as did Thun et al., a ninefold overestimate of exposure results, which more than offsets the unquantified high exposures during the early years. Based on the above analysis, the authors concluded that arsenic alone could not explain the observed excess of lung cancer deaths in this cohort.

With respect to cigarette smoking, information concerning the smoking habits of 70% of the cohort was obtained from survivors and next-of-kin. Some 77.5% for whom information was available were current or former smokers. This prevalence of "ever" smokers is close to the 72.9% prevalence noted among white males over 20 in the 1965 Health Interview Survey referred to previously. The authors pointed out that even if the percentage of heavy smokers (25+ cigarettes/day) in the cadmium cohort were double that of the 20% white male 1965 population, the rate ratio would increase by only 1.25, according to the method of Axelson (1978). Hence, the authors conclude that cigarette smoking is unlikely to account for the twofold increase in lung cancer deaths observed among workers in this cohort with 2 or more years of employment.

Besides an increase in the risk of lung cancer brought about by exposure to cigarette smoke per se, there is also potentially an added component to this risk due to the presence of cadmium in cigarette smoke. However, it is not likely that the added burden of cadmium found in cigarette smoke would have contributed in any substantial way to the risk of lung cancer already sustained by members of this cohort from the rather high concentrations of airborne cadmium found in the cadmium production plant. The earlier 1981 EPA Health Assessment Document on Cadmium estimates that a 1 pack/day smoker would retain an estimated 1.41 μg/day of cadmium in his lungs from an estimated exposure level of 2.2 μg/day, which is the equivalent of exposure to 0.28 $\mu g/m^3$ of cadmium in ambient air. Estimates derived by Smith et al. (1980) indicate that inhalation exposures in the production plant ranged from an average low of 20 $\mu g/m^3$ in the tankhouse in the period after 1960 to an average high of 1,500 $\mu g/m^3$ in the mixing department prior to 1950. Overall, it appears that the levels of airborne cadmium to which the workers of this cohort were subjected were considerably higher than those which smokers would have sustained from exposure to cadmium in cigarette smoke. Indeed, the increase in the lifetime burden of cadmium from a pack/day smoker for 40 years at 2.2 $\mu g/m^3$ of cadmium would equal only $\frac{0.28\ \mu g/m^3 \times 40\ \text{years} \times 365\ \text{days/year}}{1{,}000\ \mu g/mg} = 4.1\ \text{mg-days}/m^3$. This total additive cumulative exposure from cadmium in cigarette smoke is less than 1% of the lower limit of the cumulative exposure in which the first excess nonsignificant lung cancer risk is seen.

Of concern in this study is the possibility that the combined effect of increased cigarette smoking and exposure to arsenic might have served to produce the significant positive risk of lung cancer observed in this cohort. Such an effect is not likely to be present in this cohort.

In a study by Pinto et al. (1978) of arsenic-exposed workers at the ASARCO copper smelter, the authors actually found an inverse relationship between cigarette smoking and arsenic exposure (Table 21). In this table from the Pinto et al. (1978) study, the relationship of smoking status and the risk of dying from respiratory cancer in retired arsenic workers is presented. The SMR was actually higher at 506 in nonsmokers, but lower in smokers at 287.

TABLE 21. NUMBER OF RETIREES, OBSERVED RESPIRATORY CANCER DEATHS, AND STANDARDIZED MORTALITY RATIOS BY SMOKING STATUS OF 377 MEN ALIVE ON JANUARY 1, 1961

Smoking status	Number of retirees	Number of deaths	SMR
Smokers	189	15	287.3[a]
Ex-smokers	69	3	245.1
Nonsmokers	119	3	506.5[a]

[a] $p < 0.05$

SOURCE: Pinto et al., 1978.

On the other hand, a study by Pershagen et al. (1981) found that the synergistic effects of concurrent exposure to both cigarette smoking and arsenic exceeded the sum of the separate individual contributions. However, the Carcinogen Assessment Group (CAG) has had an opportunity to review and evaluate the Pershagen et al. (1981) case control study of 190 arsenic exposed individuals and their controls. It was found that the synergistic effect of arsenic and smoking was not statistically significant by either the Schlesselman (1982) test for synergy or by a test for interaction with a log-linear model. We judged his results to be inconclusive.

By contract, in another study by Welch et al. (1982), the effects of arsenic exposure and smoking habits of 1,800 Anaconda copper smelter workers were examined. Although the authors found an additive effect, no synergistic effect (Table 22) was found. Welch and his colleagues reported that there was a "relative lack of importance of smoking as compared to arsenic exposure." In commenting on the Pershagen (1981) case-control study, these same authors said, "Our findings contrast with those of these researchers (Pershagen et al.) in that we found no evidence of interaction, and found arsenic to be relatively more important than cigarette smoking."

Summary

Of the many epidemiologic studies of cancer in cadmium-exposed persons reviewed by the CAG, only four (Kipling and Waterhouse, 1967; Lemen et al., 1976; Holden, 1980; and Sorahan and Waterhouse, 1983) provide evidence of a statistically significant positive association ($p < 0.05$) of cadmium with prostate cancer.

Several other studies (Potts, 1965; Kjellstrom et al., 1979; McMichael et al., 1976a, b; Anderssen et al., 1982; Kjellstrom, 1982; Varner, 1983, unpublished; and Thun et al., 1985) provide the suggestion of an increased risk of prostate cancer (although statistically nonsignificant) with exposure to cadmium.

With respect to these studies, however, several comments are in order. The studies by Potts (1965), Kipling and Waterhouse (1967), Sorahan (1981), and Sorahan and Waterhouse (1983) cannot be considered independently of one another. The workers in the McMichael et al. (1976a, b) studies were subsequently shown not to have had any exposures to cadmium, and the observed excess of prostate cancer in this study was felt by Monson and Fine (1978) and Goldsmith et al. (1980) to be due to other, unexplained factors at the companies studied.

Furthermore, the significant excess risk of prostate cancer in the

TABLE 22. MORTALITY FOR RESPIRATORY CANCER FROM 1938 TO 1978 BY SMOKING HABITS AND ARSENIC EXPOSURE

Arsenic category ($\mu g/m^3$)	Smoking habits	Time weighted average				Ceiling			
		N	Obs	Exp	SMR	N	Obs	Exp	SMR
Low (< 100)	Smokers	362	7	5.8	120	297	4	4.5	88
	Nonsmokers	72	1	1.1	95	54	0	0.8	--
Medium (100-499)	Smokers	364	16	5.1	312[a]	185	2	2.6	76[a]
	Nonsmokers	71	1	1.1	89[a]	33	1	0.4	256
High (500-4,999)	Smokers	386	20	5.6	359[a]	558	31	8.3	373[a]
	Nonsmokers	77	4	1.4	286[a]	120	4	2.1	186
Very high (≥ 5,000)	Smokers	104	16	2.0	803[a]	176	22	3.0	728[a]
	Nonsmokers	20	2	0.3	620[a]	33	3	0.6	506[a]

[a] Significant at 0.01 level.

SOURCE: Welch et al., 1982.

Lemen et al. (1976) study dropped to a nonsignificant excess risk in both of the updated versions of that study (Varner, 1983 and Thun et al., 1985). Kjellstrom's "corrected healthy worker effect" risk ratio of 2.4 is nonsignificant because of the small numbers involved, although it approaches borderline significance at $p < 0.09$, offering the suggestion of a possible association of prostate cancer with cadmium exposure. However, the statistical power of most of the studies to detect an underlying twofold risk of death from prostate cancer was low. In the Thun et al. study, the power was only 34%, and when the subgroup of workers with 2 or more years of employment are looked at 20 years after initial exposure, it drops to only 15%.

Two other studies (Humperdinck, 1968 and Holden, 1969) did not report evidence of an association of prostate cancer with cadmium exposure, chiefly because the comparison population was either inadequate for the assessment of risk (Humperdinck) or absent entirely (Holden).

An update by Kjellstrom (1982) of his earlier 1979 study again failed to demonstrate a significant risk of cancer of the prostate due to cadmium. One of the failings of this study was that members of the cohort were not observed long enough to permit the evaluation of latent effects. More than half of the cohort had received no exposure to cadmium prior to 1959, and thus could not have been followed even for 20 years.

The study by Armstrong and Kazantzis (1983) of 6,994 workers also failed to demonstrate an increased risk of prostate cancer due to cadmium. This study combined cohorts from 15 different plants, each with its own unique exposure history, and none of which were necessarily comparable. Exposures to cadmium in most of these plants may have been below the level at which the study design could detect a risk.

Kolonel (1976) found a statistically significant elevated risk of renal cancer in persons occupationally exposed to cadmium, and an even greater risk in occupationally exposed people who smoke, thus raising the possibility of a synergism. The chance of selection bias and concurrent occupational exposures to nickel, lead, zinc, and a variety of metals also minimizes the importance of the findings.

With respect to a risk of prostate cancer from exposure to cadmium and its compounds, the evidence is weak at best, and is considered by the CAG to be insufficient to conclude that cadmium is a prostate carcinogen.

On the other hand, recent evidence of a significant dose-response lung cancer risk from exposure to cadmium is available from the Thun et al. (1985) study, in which the more than twofold excess risk of lung cancer seen in cadmium smelter workers was found to result from cadmium exposure rather than from the presence of arsenic in the plant or increased smoking by the workers. Thun et al. analyzed both of the above factors as potential confounders and convincingly demonstrated that the significant excess risk of lung cancer could not be due to smoking, to exposure to arsenic, or to any combination of these factors acting synergistically. The earlier version of this study, by Lemen et al. (1976), also demonstrated a significantly elevated risk of lung cancer.

Varner (1983) also found a statistically significant excess of lung cancer in his updated version of the earlier Lemen et al. study. Varner also noted a dose-response relationship for both lung cancer and total malignant neoplasms with increasing cumulative exposure. Varner indicated, however, that the significant excess is probably due to smoking or to the presence of arsenic in the plant. However, he had not had a chance to analyze their impact because his paper was preliminary.

Sorahan and Waterhouse (1983), using the SMR method, also noted a clearly statistically significant risk of lung cancer in their study population.

In addition, a significantly high test-statistic was noted for excess lung cancer utilizing the "regression models in life tables (RMLT)" method in the "high to moderately exposed" group but not in the "highest exposure" category, although the test-statistic was elevated. Sorahan suggested that the excess might be due to exposure to fumes from oxyacetylene welding. No significantly high test-statistic was found in his "highest exposure" group, however, possibly because of a lack of sensitivity due to small numbers.

In his earlier paper, Sorahan (1981) found the risk of lung cancer to be nonsignificantly elevated through SMRs calculated in a retrospective/prospective cohort study of workers who began employment before and after the amalgamation of two factories into a nickel-cadmium battery plant.

Armstrong and Kazantzis (1983) also demonstrated a significant risk of lung cancer in workers designated by them as having worked in "low exposure" jobs for a minimum of 10 years. Little sensitivity remained in the "highly exposed" group with which to detect a risk after a minimum of 10 years' employment, and such a significant risk was not shown. Furthermore, a nonsignficant excess risk was evident in the "ever mediumly" exposed group in workers with a minimum of 10 years' employment. This study, however, did not deal with latent factors 15 or 20 years after initial exposure in combination with length of employment in sufficient detail. Also, 17 different plant populations were combined to form one cohort, thus raising the possibility that very little exposure occurred to most members of the cohort. Furthermore, definitions of "ever high," "ever medium," and "always low" categories of exposure, based partially on expected cadmium urine concentrations, suggest a cohort with little exposure to cadmium.

Holden (1980) reported a significantly excess risk of lung cancer in "vicinity" workers, which he maintained could have been due to the presence of other metals, such as arsenic. No excess risk was seen in the group with the highest exposure, however. Latent factors were not considered, nor was the movement of workers from jobs with high exposure to jobs with low exposure, possibly because of seniority.

Andersson et al. (1982), in their update of the Kjellstrom et al. (1979) study, noted a slight but nonsignificant lung cancer risk in alkaline battery factory workers; however, this observation was based on only three lung cancer deaths occurring to this cohort, and the study also suffers from a "small numbers" problem. In the earlier study, Kjellstrom et al. (1979) observed a slight but nonsignificant excess of lung cancer based on two cases in the same small group of cadmium-nickel battery factory workers.

Inskip and Beral (1982) noted a slightly increased but nonsignificant risk of lung cancer among female residents of two small English villages who presumably were exposed to cadmium-contaminated soil via the oral route. However, again only a small number of lung cancers were observed.

Overall, the weight of epidemiologic evidence is limited with respect to the risk of lung cancer from exposure to cadmium and/or cadmium oxide, although not compelling with respect to finding cadmium to be a prostate carcinogen. At best, the epidemiologic evidence for the carcinogenicity of cadmium must be described as limited, according to the criteria of the IARC.

QUANTITATIVE ESTIMATION

INTRODUCTION

This quantitative section deals with the unit risk for cadmium in air and the potency of cadmium relative to other carcinogens that the Carcinogen Assessment Group (CAG) has evaluated. The unit risk estimate for an air pollutant is defined as the incremental lifetime cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 $\mu g/m^3$ of the agent in the air that they breathe. These calculations are done to estimate, in quantitative terms, the impact of the agent as a carcinogen. Unit risk estimates are used for two purposes: 1) to compare the carcinogenic potencies of several agents with each other, and 2) to give a crude indication of the population risk that would be associated with air or water exposure to these agents, if the actual exposures were known.

The data used for quantitative estimation are taken from one or both of the following: 1) lifetime animal studies, and 2) human studies where excess cancer risk has been associated with exposure to the agent. In animal studies it is assumed, unless evidence exists to the contrary, that if a carcinogenic response occurs at the dose levels used in the study, then response will also occur at all lower doses with an incidence determined by the extrapolation model.

There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards. For practical reasons, such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. We must, therefore, depend on our current understanding of the mechanisms of carcinogenesis for guidance as to which risk model to use. At the present time the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is reflected by the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal type of biological response, which is characteristic of mutagenesis, is associated with a linear nonthreshold dose-response relationship. Indeed, there is substantial evidence (from mutagenicity studies with both ionizing radiation and a wide variety of chemicals) that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, and liver cancer induced by aflatoxins in the diet). Some supporting evidence also exists from animal experiments (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin). Linearity is also supported when the mode of action of the carcinogen in question is similar to that of the background cancer occurrence in the exposed population.

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, a linear nonthreshold model has been adopted as the primary basis for estimating risk at low levels of exposure. The risk estimates made with this model should be regarded as conservative, representing the most plausible upper limit for the risk, i.e., the true risk is not likely to be higher than the estimate, but it could be lower.

For several reasons, the unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans compared to animals on a mg/surface area basis is virtually without experimental verification regarding carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns, and other cultural factors.

The unit risk estimate can give a rough indication of the relative potency of a given agent as compared with other carcinogens. Comparative potency estimates for different agents are more reliable when the comparisons are based on studies in the same test species, strain, and sex, and by the same route of exposure, preferably inhalation.

The quantitative aspect of carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process, e.g., in setting regulatory priorities, evaluating the adequacy of technology-based controls, etc. However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk. The risk estimates presented in subsequent sections should not be regarded as accurate representations of the true cancer risks even when the exposures are accurately defined. However, the estimates presented may be factored into regulatory decisions to the extent that the concept of upper risk limits is found to be useful.

The mathematical formulation chosen to describe the linear nonthreshold dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data, and it incorporates a procedure for estimating the largest possible linear slope (in the 95% confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment.

In addition to the multistage model currently used by the CAG for low-dose extrapolation (a detailed description of the procedure is given in Appendix A), three more models, the probit, the Weibull, and the one-hit, are employed for purposes of comparison. These models cover almost the entire spectrum of risk estimates that could be generated from the existing mathematical extrapolation models. The models are generally statistical in character and are not derived from biological arguments, except for the multistage model, which has been used to support the somatic mutation hypothesis of carcinogenesis (Armitage and Doll, 1954; Whittemore, 1978; Whittemore and Keller, 1978).

The main difference among the above models is the rate at which the response function P(d) approaches zero or P(0) as dose d decreases. For instance, the probit model would usually predict a smaller risk at low doses than the multistage model because of the difference of the decreasing rate in the low-dose region. However, it should be noted that the multistage model could always be artificially made to have the same (or even greater) rate of decrease as the probit model, by making some dose transformation and/or by assuming that some of the parameters in the multistage model are zero. This, of course, is not reasonable without knowing, a priori, what the carcinogenic process for the agent is.

Although the multistage model appears to be the most reasonable or at least the most general model to use, the point estimates generated from this model are of limited value because of uncertainty as to the shape of the dose-response curve beyond the experimental exposure levels. Furthermore, the point estimates at low doses extrapolated beyond the experimental dose could be extremely unstable and could differ drastically, depending on the size of the lowest experimental dose. Since the upper-bound estimates at low doses from the multistage model are relatively more stable than the point estimates, the CAG suggests that the upper-bound estimate of the risk (or the lower-bound estimates of the dose) be used in evaluating the carcinogenic potency of a suspect carcinogen. The upper-bound estimate can be taken as a plausible estimate if the true dose-response curve is actually linear at low doses. The upper-bound estimate means that the risks are not likely to be higher but could be lower if the compound has a concave upward dose-response curve or a threshold at low doses. Another reason why, at best, only an upper-bound estimate of the risk can be obtained when animal data are used is that the estimated risk is no more than conditional probability under the assumption that an animal carcinogen is also a human carcinogen. Therefore, in reality, the actual risk could range from a value near zero to an upper-bound estimate.

PROCEDURES FOR DETERMINING CARCINOGENIC POTENCY

Description of the Low-Dose Animal Extrapolation Model

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\left[-(q_0 + q_1 d^2 + \ldots + q_k d^k)\right]$$

where

$$q_i \geq 0, \; i = 0, 1, 2, \ldots, k$$

Equivalently,

$$P_t(d) = 1 - \exp [-(q_1 d + q_2 d^2 + \ldots + q_k d^k)]$$

where

$$P_t(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate at dose d or the effect of treatment.

The point estimate of the coefficients q_i, i = 0, 1, 2, ..., k, and consequently the extra risk function $P_t(d)$ at any given dose d, is calculated by maximizing the likelihood function of the data.

The point estimate and the 95% upper confidence limit of the extra risk $P_t(d)$ are calculated by using the computer program GLOBAL83 (Howe, 1983), which is an update to the computer program GLOBAL79, originally developed by Crump and Watson (1979). At low doses, upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit, q_1^*, on parameter q_1. Whenever $q_1 > 0$, at low doses the extra risk $P_t(d)$ has approximately the form $P_t(d) = q_1^* \times d$. Therefore, $q_1^* \times d$ is a 95% upper confidence limit on the extra risk, and R/q_1^* is a 95% lower confidence limit on the dose producing an extra risk of R. Let L_0 be the maximum value of the log-likelihood function. The upper limit, q_1^*, is calculated by increasing q_1 to a value of q_1^* such that when the log-likelihood is remaximized subject to this fixed value q_1^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation

$$2\ (L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, which corresponds to a 95% upper-limit (one-sided). This approach of computing the upper confidence limit for the extra risk $P_t(d)$ is an improvement on the Crump et al. (1977) model. The upper confidence limit for the extra risk calculated at low doses is always linear. This is conceptually consistent with the linear nonthreshold concept discussed earlier. The slope, q_1^*, is taken as an upper bound of the potency of the chemical in inducing cancer at low doses. (In the section calculating the risk estimates, $P_t(d)$ will be abbreviated as P.) In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment, including the control group.

Whenever the multistage model does not fit the data sufficiently well, data at the highest dose is deleted, and the model is refitted to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square statistic

$$X^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i \ (1-P_i)}$$

is calculated where N_i is the number of animals in the i^{th} dose group, X_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is determined to be unacceptable whenever X^2 is larger that the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients.

Selection of Data--

For some chemicals, a number of studies in different animal species, strains, and sexes, each run at varying doses and routes of exposure, are available. A choice must be made as to which of the data sets is appropriate for use with the model. It may also be necessary to correct for metabolism differences between species and absorption factors via different routes of administration. The following procedures have been used by the CAG in evaluating these particular data; they are consistent with the approach of making a maximum-likely risk estimate.

1. The data on tumor incidence are separated according to organ sites or tumor types. The dose and tumor incidence data set used in the model is the set in which the incidence is statistically significantly higher than in controls for at least one test dose level, and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of small numbers of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the data set having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers A_1, A_2, ..., A_m is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$$

3. If two or more significant tumor sites are observed in the same study,

and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

Calculation of Human Equivalent Dosages from Animal Data--

Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere, the exposure in mg day/two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment this equivalent dose is computed in the following manner: Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e., during l_e), and

W = average weight of the experimental animal

Then, the lifetime average exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

Inhalation--When exposure is via inhalation, the dose for inhaled particulate matter, in mg/day, can be expressed as

$$m = I \times v \times f$$

where I = the volume of air inspired/day in m^3, v = mg/m^3 of the agent in air, and f = the fraction deposited in the lungs.

The inhalation rates, I, for various species can be calculated from the observations of the Federation of American Societies for Experimental Biology (1974) that 25-g mice breathe 34.5 liters/day and 113-g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

For humans, the value of 20 m^3/day is adopted as a standard breathing rate. The equivalent exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air per kg per day, $i = I/W$, based upon the previously stated relationship, are tabulated as follows:

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.64
Mice	0.03	1.3

Therefore, for particulate matter, the equivalent exposure in $mg/W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivf}{W^{2/3}} = \frac{iWvf}{W^{2/3}} = iW^{1/3}vf$$

The fraction of inhaled particles deposited in the lung will vary with species, particle size, rate and depth of respiration, etc. In the only animal inhalation study available for conducting a risk assessment on cadmium (Takenaka et al., 1983), the mean particle size of the aerosol was 0.55 µm in diameter. Raabe et al. (1977) reported, for rats inhaling particles in this size range, that 10% was deposited in the gas exchange regions of the lungs, with an additional 3% deposited in the conducting airways. In different human studies in which 0.5 μm diameter particles were inhaled, the fraction deposited in the deep lung varied from ≈ 9% to 21% (Lippman, 1977). In the human studies, considerable variability was noted, not only among studies, but among individuals within a study and within individuals due to changes in breathing patterns. Since a considerable degree of variability in deposition fractions along with minimal differences between the means of the rat study and the human studies occurred, an adjustment for dose between rats and humans based upon deposition efficiency was not considered appropriate.

The fraction of particles deposited in the deep lung will also vary with particle size. An adjustment in dose would be indicated if cadmium particles in ambient air differ markedly in size from those used in the appropriate animal exposure study. Unfortunately, precise data is unavailable. In studies of point source emissions, however, cadmium was shown to be concentrated in the smallest particles. For example, 66% of cadmium-containing particles emitted from municipal incinerators were less than 2 μm in diameter, with a median diameter of less than 1 μm (Jacko and Neuendorf, 1977). Trace metals, including cadmium, were also concentrated in the smallest fly ash particles emitted from electric power generating plants (Natusch et al., 1973). The data from point sources indicate that cadmium-containing particles in ambient air, while very small, are probably somewhat larger and more variable in size than those used in the Takenaka et al. (1983) study. Since cadmium or cadmium compounds, however, are seldom present in ambient particulates in a pure state, and since cadmium concentration is greater in the smallest particles, it was again considered inappropriate to adjust for deposited dose based upon particle size.

A third factor possibly influencing dose is residence times of particulate matter in the lungs. A longer residence time may allow less soluble forms of cadmium to be leached from the particles, thereby increasing bioavailability. Clearance half-times for cadmium particles deposited in the alveolar region have been reported to vary from about 60 days in rats (Oberdoerster et al., 1979) to 225 days for dogs (Oberdoerster and Morrow, 1983) and even longer for primates (Oberdoerster, 1984). Based on this information, it would appear that humans may be at greater risk than rats following inhalation of relatively insoluble cadmium compounds.

Although the data available do not provide definitive information for making an adjustment in dose based on any of the individual factors discussed, collectively the data suggest that humans could be at somewhat greater risk than rats exposed to similar cadmium aerosols. Ambient air particulates, however, are considerably different from those used experimentally. In the Takenaka et al. (1983) study, the cadmium chloride aerosol used was quite soluble. As an indication of this, tumors were found in the bronchial region where clearance half-times were less than one day. While there is little direct information relating to the bioavailability of cadmium in ambient air particulate matter, on the basis of information regarding solubility of fly ash and other point source particle emissions, it appears that cadmium is likely to be much less bioavailable than in the chloride form. As a result, it was felt that a unit risk estimate based upon the Takenaka et al. (1983) study with no adjustment for deposition fraction or bioavailability was sufficiently conservative to protect human populations.

Calculation of the Unit Risk from Animal Data--

The 95% upper-limit risk associated with d mg/kg$^{2/3}$/day is obtained from GLOBAL83 and, for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of $X = 1$. This value is estimated by finding the number of $mg/kg^{2/3}/day$ that corresponds to one unit of X and substituting this value into the above relationship. Thus, for example, if X is in units of $\mu g/m^3$ in the air, we have $d = 0.29 \times 70^{1/3} \times 10^{-3}$ $mg/kg^{2/3}/day$. Note that an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures and then increase the j^{th} polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \qquad j = 1, 2, \ldots, k$$

and use mg/kg equivalents for the unit risk values.

UNIT RISK ESTIMATES FOR CADMIUM

Unit Risk Estimate Based on an Animal Study

The bioassay by Takenaka et al. (1983) using male Wistar rats and cadmium chloride aerosol was chosen for estimating the quantitative unit risk of cadmium. This was the only positive animal inhalation study with cadmium and/or cadmium compounds that showed a dose-response trend of primary lung carcinomas in animals continuously exposed to cadmium chloride aerosols for 18 months. The primary lung carcinomas were histologically differentiated as adenocarcinomas, epidermoid carcinomas, combined epidermoid and adenocarcinomas, and mucoepidermoid carcinomas, but were combined for this unit risk analysis. The incidences of total primary lung carcinomas was 15% (6/39), 53% (20/38), and 71% (25/35) for the low (12.5 $\mu g/m^3$), medium (25 $\mu g/m^3$), and high (50 $\mu g/m^3$) exposure groups, respectively. No tumors were found among 38 controls.

In arriving at an upper-limit unit risk estimate for humans, dose is calculated on a lifetime continuous basis with 2 years considered a full lifetime exposure for rats. Thus, by multiplying by 0.75 the measured concentrations of

13.4 μg/m^3, 25.7 μg/m^3, and 50.8 μg/m^3 elemental cadmium for the three dose groups, the lifetime continuous exposure can be estimated as 10.05 μg/m^3, 19.3 μg/m^3, and 38.1 μg/m^3, respectively. The corrections for animal to human weight differences are given below.

In transforming from animal exposure to human equivalence, the method for treating inhalation of an aerosol (presented earlier in the section for calculation of human equivalent dosages from animal data), assumes aerosols to be deposited proportionally to the volume of air inspired. The volume of air inspired for 113-g rats is 0.105 m^3/day (Federation of American Societies for Experimental Biology, 1974). For the Wistar rats used in the Takenaka et al. bioassay, the average weights at 18 months were 424.6 g (for the 13.4 μg/m^3 group), 437.6 g (for the 25.7 μg/m^3 group), and 424.3 g (for the 50.8 μg/m^3 group). To adjust for these weights the following formula is used:

$$I = 0.105 \, (W/0.113)^{2/3} \text{ m}^3/\text{day}$$

where I = the daily volume of air inhaled for a rat weighing W kilograms. For the low, medium, and high exposure groups, the I values are 0.254 m^3/day, 0.259 m^3/day, and 0.254 m^3/day, respectively. Combining these with the lifetime continuous exposure estimates above, daily exposure is estimated to be 2.55 μg/day, 5.00 μg/day, and 9.68 μg/day, respectively. Equivalently, dose can be estimated on a μg/kg/day basis as 6.0 μg/kg/day, 11.4 μg/kg/day, and 22.8 μg/kg/day.

Based on the above data for animals, the 95% upper-limit unit risk of cancer resulting from elemental cadmium in cadmium chloride exposure is $q_1^* = 6.3 \times 10^{-2} (\mu g/kg/day)^{-1}$ using the linearized multistage model. When transformed to equivalent human dose, the CAG method requires multiplying q_1^* by the weight ratio factor $(W_h/W_a)^{1/3}$, where W_h = weight of a human, which is assumed to be 70 kg, and W_a is the mean weight of the animals; thus,

$$q_h^* = q_1^* (W_h/W_a)^{1/3} = 6.3 \times 10^{-2} (70/0.429)^{1/3} = 3.4 \times 10^{-1} (\mu g/kg/day)^{-1}$$

Using the linearized multistage model, the 95% upper-limit unit risk estimate for induced cancers based on elemental cadmium exposure is $q_h^* = 3.4 \times 10^{-1}$. If it is assumed that cadmium chloride is the carcinogenic agent and not the cadmium ion, an adjustment must be made for the weight of the two cadmium chloride ions. In that case, the molecular weight contribution of cadmium to the total molecular weight is 112.4/183.3 = 0.613. The interpretation in terms of risk is that a q_h^* for inhalation of cadmium chloride is

$$q_h^* = 3.4 \times 10^{-1} (\mu g/kg/day)^{-1} \times 0.613 = 2.1 \times 10^{-1} (\mu g/kg/day)^{-1}$$

This can be converted back to human exposure in terms of $\mu g/m^3$ by assuming that a human weighing 70 kg breathes 20 m^3 of air per day. Thus,

$$q_h^* = 2.1 \times 10^{-1} (\mu g/kg/day)^{-1} \times \frac{1}{70\ kg} \times \frac{20\ m^3}{day} = 6.0 \times 10^{-2} (\mu g/m^3)^{-1}$$

for cadmium ion exposure, and

$$q_1^* = 3.4 \times 10^{-1} (\mu g/kg/day)^{-1} \times \frac{1}{70\ kg} \times \frac{20\ m^3}{day} = 9.7 \times 10^{-2} (\mu g/m^3)^{-1}$$

based on inhalation exposure to the cadmium ion. Therefore, the incremental unit risk from the inhalation of 1 μg of elemental cadmium per m^3 of air is approximately

$$R = 1 - \exp -(0.097 \times 1) = 0.092$$

This is an upper-bound estimate of risk based on the direct experimental evidence presently available. Using other dose-response models to estimate risk (as shown in Appendix A) can give considerably lower estimates than those obtained using the upper-bound multistage model. However, there is no direct evidence suggesting that these alternative models provide a more rational basis for estimating risk than the upper-bound multistage model. It must be kept in mind that the alternative models have the potential for seriously underestimating the true risk at low levels of environmental exposure to cadmium.

Unit Risk Estimate Based on a Human Study

Data Base--

At the present time the strongest evidence in humans suggesting a cadmium-induced carcinogenic response is found in the Thun et al. (1985) study. This response was observed in a cohort of cadmium smelter workers who were hired on or after January 1, 1926, and were employed for at least 2 years in a production capacity in the same plant from January 1, 1940, to December 31, 1969. This cohort of white males had a total of 16 respiratory cancer deaths through December 31, 1978, while only 6.99 would be expected based on calendar time age-specific respiratory cancer death rates for U.S. white males. Assuming that the U.S. white male population is a valid control population for the cohort of cadmium smelter workers, the probability of obtaining 16 or more respiratory cancer deaths, if there was no effect due to cadmium, is only 0.0024, based on the exact Poisson test.

Thun et al. (Table 9, page 29 of their paper) divided the cohort of white males hired on or after January 1, 1926, into three groups based on cumulative exposure. This cohort included individuals with less than 2 years of exposure. In an April 10, 1984, letter from Thun to the U.S. EPA, the approximate midpoints of the exposure intervals were given. The data shown in Table 23 were generated using these two sources of information. The exposure (in terms of 24 hours $\mu g/m^3$-years) needed to estimate environmental risk is obtained under the assumption of 8 hours worked per day, 240 days per year, and is shown in column 3 of Table 23. It should be noted that the 240/365 adjustment is required because Thun et al. computed exposure days on the basis of elapsed calendar time in an exposure category, not on the basis of working days.

A number of problems arise in using these data to obtain a quantitative estimate of human respiratory cancer risk due to cadmium exposure. Among them are the following:

1. There is some evidence that the smoking rate for the cadmium workers was higher than that of the general white male population.
2. The exposure to cadmium is confounded with exposure to arsenic, a known respiratory carcinogen.
3. Very limited evidence exists concerning the exposure rate and the duration of exposure for the members of the cohort.
4. No exposure estimates exist for individuals.
5. The extent of the deviations of the exposure estimates from the actual exposure is unknown.

In March 1985, Thun began a new study with ARSARCO to obtain estimates of individual exposures to cadmium, arsenic, and, where possible, cigarette smoke for the cohort he had originally studied. This new study could considerably reduce the severity of the problems cited previously, and could be critical in evaluating the potency of cadmium. At a minimum, it should be a valuable source of data for use in testing the hypothesis that the observed increases in respiratory cancer rate are due to confounding effects of arsenic and cigarette

TABLE 23. BASIC DATA USED FOR ESTIMATING UNIT RISK

Cumulative exposure (mg/days/m^3)	Median[a] observation in interval	24-hour/$\mu g/m^3$[b] equivalent X_j	Expected ICD 162-163[c] assuming no cadmium effect Eo_j	Observed number of deaths ICD 162-163 O_j
$\leq$ 584	280	168	3.77	2
585-2920	1210	727	4.61	7
$\geq$ 2921	4200	2522	2.50	7

[a] Provided by Thun (letter dated April 10, 1984).
[b] Median observation multiplied $10^3 \times 8/24 \times 1/365 \times 240/365$.
[c] $Eo_j = O_j \times 10^2 \div SMR_j$.

SOURCE: Thun et al., 1985.

smoke rather than cadmium. Unfortunately, this information is not expected in the near term.

Without such data, the approach taken to estimate unit risk assumes that the entire observed effect is due to cadmium. Several factors suggest that this approach is not unreasonable. First, if the effect were due to a differential smoking rate between the study cohort and the general population, one would expect to see an elevated risk in all exposure groups for smoking-caused diseases. This was not the case. The lowest exposure group had a relative risk (for respiratory cancer) of only 2/3.77 = 53.1%, as indicated in Table 23. Also, as shown in Table 3, page 23 of the Thun et al. (1985) paper, the relative risk for diseases of the circulatory system (ICD 400-468) is only 65, suggesting no elevated cigarette use.

Second, Brown and Chu (1982) offer highly suggestive evidence that arsenic is a late-stage carcinogen. As a result, the risks 10 to 15 years after the cessation of exposure to arsenic are not expected to be highly elevated. Arsenic exposure, for the most part, was terminated 20 or more years prior to the observed lung cancer cases in the Thun et al. cohort. This fact argues against arsenic being a major contributor to the elevated respiratory cancer rates observed in the Thun et al. cohort.

However, it must be recognized that while these arguments are reasonable, they are no substitute for real data, and the upper-bound estimates for cadmium cancer risk presented in the following section could be considerably altered when the results of Thun's new study become available.

Model Used--

To estimate lifetime risk from the data shown in Table 23, the simplest possible model that can be used with this level of information is assumed.

It is postulated that the age-specific rate at any point in time is increased by an amount proportional to the cumulative exposure up to that point in time. This implies that

$$h(t) = \Delta X$$

where X is cumulative exposure and Δ is the proportional increase. If exposure is constant from time o to t at level x, it follows that

$$h(t) = \Delta xt$$

The preceding model is one of the models used in the BEIR III report (National Research Council, 1980) to estimate risk due to ionizing radiation. This model is also equivalent to assuming a two-stage model with only the first stage affected by exposure. As a first approximation, it is assumed that the total median cumulative exposure for each group can be related to each year of the observation period for that group. This assumption would tend to overestimate exposure and thus underestimate risk. However, the bias is less than a factor of two since using the lower bounds would not increase the estimate more than that. Under the assumed model the total expected number of cases in the observation period for the jth exposure group may be expressed as

$$E_j = Eo_j + \Delta X_j W_j$$

where Eo_j is the expected number of cases due to background causes, X_j is cumulative exposure, and W_j is the number of person-years of observation for the jth exposure group. The observed number of cases in the jth exposure group is a Poisson random variable with mean E_j under the assumed model. Thus, the likelihood of the observed results may be expressed as

$$L \prod_{j=1}^{3} e^{-[Eo_j + \Delta X_j W_j]} [Eo_j + \Delta X_j W_j]^{O_j} / O_j!$$

where O_j is the observed number of cases in the jth exposure group. The maximum likelihood estimate of the unknown parameter Δ is obtained by solving the equation

$$\frac{d\ln L}{d\Delta} = \sum_{j=1}^{3} - X_j W_j + \frac{O_j X_j W_j}{Eo_j + \Delta X_j W_j} = 0$$

for Δ.

the asymptotic variance for the parameter Δ, is

$$-E\left[\frac{d^2 \ln L}{d^2\Delta}\right]^{-1} = \left[\sum_{j=1}^{3} \frac{X_j^{2} W_j^{2}}{(Eo_j + \Delta x_j W_j)}\right]^{-1}$$

This variance can then be used to obtain an approximate 95% upper bound for the parameter Δ. In Table 24 the data used to obtain the estimate of Δ and its variance are shown.

TABLE 24. DATA USED TO ESTIMATE Δ AND ITS VARIANCE

Cumulative exposure X_j	Person-years observation W_j	Background expected Eo_j	Observed O_j	X_jW_j	$X_jW_jO_j$
168	7005	3.77	2	1.18×10^6	2.35×10^6
727	5825	4.61	7	4.23×10^6	29.63×10^6
2522	2214	2.50	7	5.58×10^6	39.09×10^6
				$\sum = 10.99 \times 10^6$	

An estimate of $\Delta^* = \Delta \times 10^6$ is obtained from the equation

$$10.99 = \frac{2.35}{3.77 + 1.18\,\Delta^*} + \frac{29.63}{4.61 + 4.23\,\Delta^*} + \frac{39.09}{2.50 + 5.58\,\Delta^*}$$

which has the solution $\Delta^* = 0.642$ so that $\Delta = 6.42 \times 10^{-7}$. The $V(\Delta)$ is estimated to be $V(\Delta) \simeq 1.27 \times 10^{-13}$ so that $\sqrt{V(\Delta)} \simeq 3.56 \times 10^{-7}$, and the 95% upper and 5% lower confidence bounds are approximately $\Delta_{\mu} = 12.26 \times 10^{-7}$ and $\Delta_{\ell} = 0.58 \times 10^{-7}$, respectively. It should be noted that this measure of variability only takes into account random sampling error. It does not account for potential error due to an assumed incorrect model or biased exposure estimates.

To show how a different assumed model could influence risk estimates, the following ad-hoc "threshold" model can be considered. This model is not based on any biological information. It simply uses the highest dose group with no observable statistically elevated risk as the threshold and assumes linearity in accumulated dose beyond that point. It is assumed that

$$h(t) = \begin{cases} 0 & X < 1754 \\ \Delta\,(X - 1754) & 1754 < X \end{cases}$$

where 1754, the guessed-at threshold, is the boundary point of the maximum exposed group in $\mu g/m^3$-years. For this model an estimate of Δ is

$$\Delta = (7 - 2.5) \div (2522 - 1754) \times 2214 = 2.65 \times 10^{-6}$$

In Table 25 the fit of each model is shown and evaluated using the X^2 goodness-of-fit test.

We note that both the "threshold" and linear models give an adequate fit to the data. As a result, arguments other than purely statistical must be used to select the appropriate model.

TABLE 25. GOODNESS-OF-FIT MODELS FITTED TO THE THUN DATA

Exposure interval $\mu g/m^3$-years midpoint	Number of cases expected under linear model using as the estimate of parameter Δ the			Expected number of cases under threshold model	Observed
	Lower bound	MLE	Upper bound	$\Delta = 2.65 \times 10^{-6}$ if $X > 1754$ $\Delta = 0$ if $X < 1754$	
< 350 (168)	3.84	4.53	5.21	3.77	2
351-1754 (727)	4.85	7.33	9.80	4.61	7
> 1754 (2522)	2.82	6.08	9.34	7.00	7
	χ^2 goodness-of-fit statistic				
	7.971	1.567	3.364	2.070	

SOURCE: Thun, letter of April 10, 1984; Thun et al., 1985.

Use of Parameter Estimates of Δ to Estimate Unit Risk--

Mathematically, the risk due to a constant lifetime exposure of x ppm in the air may be expressed as

$$P(x) = \int_0^\infty \{h_2(x,t)e^{-\int_0^t [h_2(x,v) + h_1(v)]dv}\}dt$$

where $h_2(x,t)$ is the age-specific death rate at age t due to a constant lifetime exposure at level x, and $h_1(t)$ is the age-specific death rate for all other causes. See Gail (1975) for a derivation of this result.

In the present situation

$$h_2(x,t) = 6.42 \times 10^{-7} \cdot xt$$

for the linear model and

$$h_2(x,t) = \begin{cases} 0 & xt < 1754 \\ 2.65 \times 10^{-6} \cdot [xt-1754] & 1754 < xt \end{cases}$$

for the "threshold" model.

Using these models and the assumption that $h_1(t)$ is the same as the overall rates in the United States in 1978 (the most recent year for which complete vital statistics data are available), the lifetime cancer risks for various constant exposure levels of cadmium have been calculated and are shown in Table 26.

Recommended Unit Risk Estimate--

A number of approaches have been used to obtain unit risk estimates. It is suggested that if a single estimate of unit risk is desired, it be based on the MLE of the linear parameter obtained from human data. This results in a

TABLE 26. ESTIMATED RISKS FOR VARIOUS MODELS BASED ON THUN DATA

Model used	Risk due to a constant lifetime exposure of		
	$1\ \mu g/m^3$	$10\ \mu g/m^3$	$100\ \mu g/m^3$
Linear nonthreshold			
Upper bound	3.5×10^{-3}	3.4×10^{-2}	2.9×10^{-1}
MLE	1.8×10^{-3}	1.8×10^{-2}	1.7×10^{-1}
Lower bound	1.7×10^{-4}	1.7×10^{-3}	1.6×10^{-2}
Threshold model	0.0	0.0	3.7×10^{-1}
April 1984 model[a]	1.9×10^{-3}	1.9×10^{-2}	1.7×10^{-1}

[a] Used in the External Review Draft of the Updated Mutagenicity and Carcinogenicity Assessment of Cadmium, prepared by the Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, April 1984.

SOURCES: Thun, letter of April 10, 1984; Thun et al., 1985.

unit risk estimate of 1.8×10^{-3}. A higher estimate of 3.5×10^{-3} would be obtained if the 95% upper bound of the parameter were used. However, it is felt that this is an unnecessary added level of conservatism, since the model used already inflates the risk estimate if nonlinear components exist or confounding factors are present.

The unit risk estimate based on the animal bioassay, 9.2×10^{-2}, also gives a higher estimate. However, species differences and cadmium form differences make an estimate from this source intrinsically less reliable than the one derived from the assumed human exposures. In addition, it must be kept in mind that these are upper-bound estimates. The true unit risk could range from this upper bound to a very small value approaching zero.

RELATIVE POTENCY

One of the uses of the concept of unit risk is to compare the relative potencies of carcinogens. For the purposes of the present analysis, potency is defined as the linear portion of the dose-response curve, and is used to calculate the required unit risk factors. In this section, the potency of cadmium is compared with that of other chemicals that the CAG has evaluated as suspect carcinogens. To estimate the relative potency on a per mole basis, the unit risk slope factor is multiplied by the molecular weight and the resulting number, expressed in terms of $(\text{mmol/kg/day})^{-1}$, is called the relative potency index.

Figure 2 is a histogram representing the frequency distribution of relative potency indices for 54 chemicals that have been evaluated by the CAG as suspect carcinogens. The actual data summarized by the histogram are presented in Table 27. Where human data have been available for a compound, such data have been used to calculate these indices. Where no human data have been

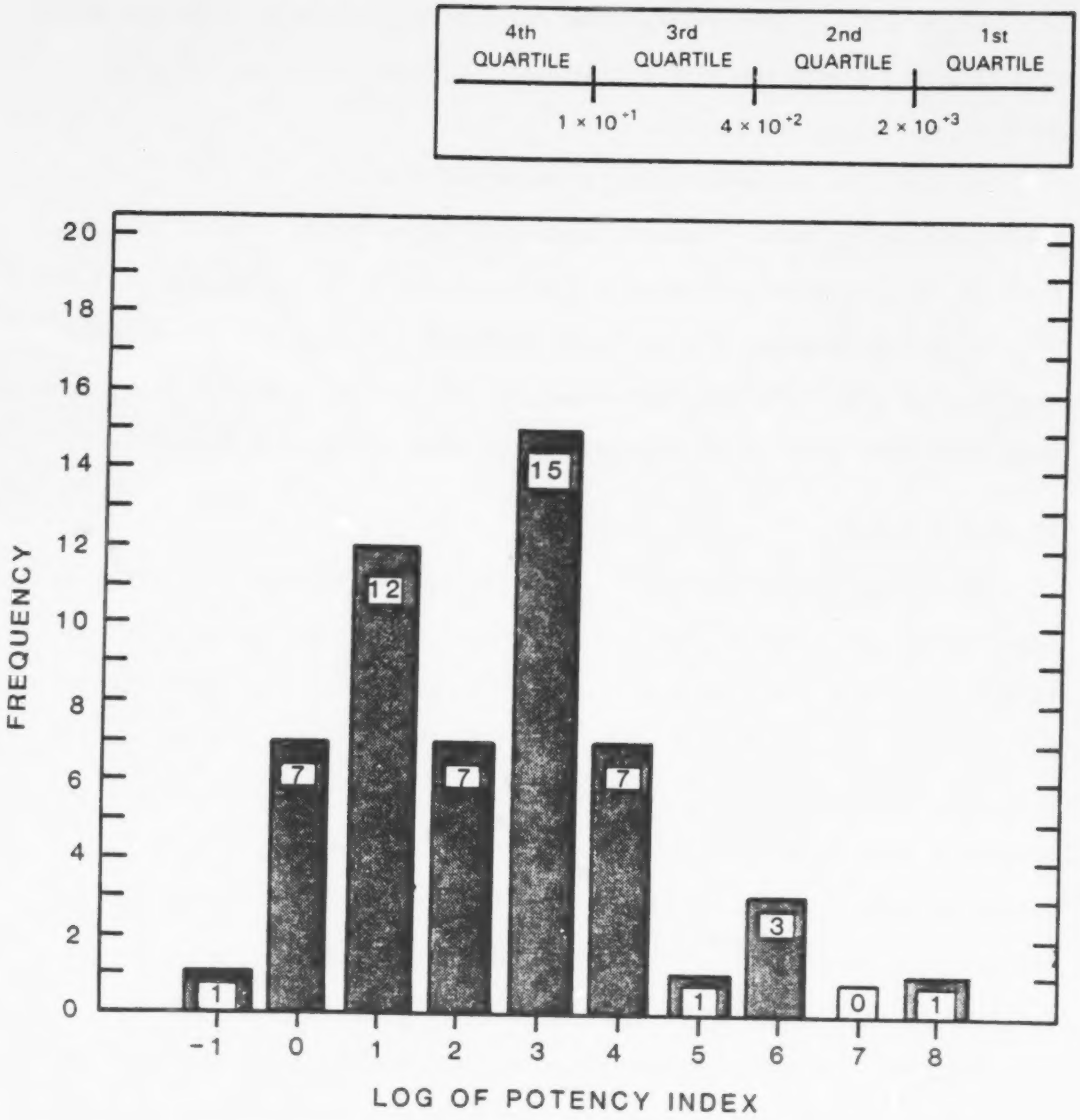

Figure 2. Histogram representing frequency distribution of the potency indices of 54 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 27. RELATIVE CARCINOGENIC POTENCIES AMONG 54 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on IARC criteria	Slope $(mg/kg/day)^{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
Acrylonitrile	107-13-1	L	S	2A	0.24(W)	53.1	$1x10^{+1}$	+1
Aflatoxin B_1	1162-65-8	L	S	2A	2900	312.3	$9x10^{+5}$	+6
Aldrin	309-00-2	I	L	2B	11.4	369.4	$4x10^{+3}$	+4
Allyl chloride	107-05-1				$1.19x10^{-2}$	76.5	$9x10^{-1}$	0
Arsenic	7440-38-2	S	I	1	15(H)	149.8	$2x10^{+3}$	+3
B[a]P	50-32-8	I	S	2B	11.5	252.3	$3x10^{+3}$	+3
Benzene	71-43-2	S	S	1	$2.9x10^{-2}$(W)	78	$2x10^{0}$	0
Benzidene	92-87-5	S	S	1	234(W)	184.2	$4x10^{+4}$	+5
Beryllium	7440-41-7	L	S	2A	2.6	9	$2x10^{+1}$	+1
1,3-Butadiene	106-99-0	I	S	2B	$1.0x10^{-1}$(I)	54.1	$5x10^{0}$	+1
Cadmium	7440-43-9	L	S	2A	6.1(W)	112.4	$7x10^{+2}$	+3
Carbon tetrachloride	56-23-5	I	S	2B	$1.30x10^{-1}$	153.8	$2x10^{+1}$	+1
Chlordane	57-74-9	I	L	3	1.61	409.8	$7x10^{+2}$	+3

(continued on the following page)

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

TABLE 27. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on IARC criteria	Slope (mg/kg/day)-1	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
Chlorinated ethanes								
1,2-Dichloroethane	107-06-2	I	S	2B	9.1×10^{-2}	98.9	9×10^{0}	+1
hexachloroethane	67-72-1	I	L	3	1.42×10^{-2}	236.7	3×10^{0}	0
1,1,2,2-Tetrachloroethane	79-34-5	I	L	3	0.20	167.9	$3\times10^{+1}$	+1
1,1,2-Trichloroethane	79-00-5	I	L	3	5.73×10^{-2}	133.4	8×10^{0}	+1
Chloroform	67-66-3	I	S	2B	7×10^{-2}	119.4	8×10^{0}	+1
Chromium VI	7440-47-3	S	S	1	41(W)	100	$4\times10^{+3}$	+4
DDT	50-29-3	I	S	2B	0.34	354.5	$1\times10^{+2}$	+2
Dichlorobenzidine	91-94-1	I	S	2B	1.69	253.1	$4\times10^{+2}$	+3
1,1-Dichloroethylene (Vinylidene chloride)	75-35-4	I	L	3	1.16(I)	97	$1\times10^{+2}$	+2
Dichloromethane (Methylene chloride)	75-09-2	I	L	3	6.3×10^{-4}(I)	84.9	5×10^{-2}	-1
Dieldrin	60-57-1	I	S	2B	30.4	380.9	$1\times10^{+4}$	+4
2,4-Dinitrotoluene	121-14-2	I	S	2B	0.31	182	$6\times10^{+1}$	+2
Diphenylhydrazine	122-66-7	I	S	2B	0.77	180	$1\times10^{+2}$	+2
Epichlorohydrin	106-89-8	I	S	2B	9.9×10^{-3}	92.5	9×10^{-1}	0
Bis(2-chloroethyl)ether	111-44-4	I	S	2B	1.14	143	$2\times10^{+2}$	+2

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

(continued on the following page)

TABLE 27. (continued)

Compounds	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope (mg/kg/day)$^{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
		Humans	Animals					
Bis(chloromethyl)ether	542-88-1	S	S	1	9300(I)	115	$1\times10^{+6}$	+6
Ethylene dibromide (EDB)	106-93-4	I	S	2B	41	187.9	$8\times10^{+3}$	+4
Ethylene oxide	75-21-8	L	S	2A	3.5×10^{-1}(I)	44.1	$2\times10^{+1}$	+1
Heptachlor	76-44-8	I	S	2B	3.37	373.3	$1\times10^{+3}$	+3
Hexachlorobenzene	118-74-1	I	S	2B	1.67	284.4	$5\times10^{+2}$	+3
Hexachlorobutadiene	87-68-3	I	L	3	7.75×10^{-2}	261	$2\times10^{+1}$	+1
Hexachlorocyclohexane								
technical grade					4.75	290.9	$1\times10^{+3}$	+3
alpha isomer	319-84-6	I	S	2B	11.12	290.9	$3\times10^{+3}$	+3
beta isomer	319-85-7	I	L	3	1.84	290.9	$5\times10^{+2}$	+3
gamma isomer	58-89-9	I	L	2B	1.33	290.9	$4\times10^{+2}$	+3
Hexachlorodibenzodioxin	34465-46-8	I	S	2B	$6.2\times10^{+3}$	391	$2\times10^{+6}$	+6
Nickel	7440-02-0	L	S	2A	1.15(W)	58.7	$7\times10^{+1}$	+2
Nitrosamines								
Dimethylnitrosamine	62-75-9	I	S	2B	25.9(not by q_1^*)	74.1	$2\times10^{+3}$	+3
Diethylnitrosamine	55-18-5	I	S	2B	43.5(not by q_1^*)	102.1	$4\times10^{+3}$	+4
Dibutylnitrosamine	924-16-3	I	S	2B	5.43	158.2	$9\times10^{+2}$	+3

(continued on the following page)

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

TABLE 27. (continued)

Compounds	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope (mg/kg/day)-1	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
		Humans	Animals					
N-nitrosopyrrolidine	930-55-2	I	S	2B	2.13	100.2	$2\times10^{+2}$	+2
N-nitroso-N-ethylurea	759-73-9	I	S	2B	32.9	117.1	$4\times10^{+3}$	+4
N-nitroso-N-methylurea	684-93-5	I	S	2B	302.6	103.1	$3\times10^{+4}$	+4
N-nitroso-diphenylamine	86-30-6	I	S	2B	4.92×10^{-3}	198	1×10^{0}	0
PCBs	1336-36-3	I	S	2B	4.34	324	$1\times10^{+3}$	+3
Phenols								
2,4,6-Trichlorophenol	88-06-2	I	S	2B	1.99×10^{-2}	197.4	4×10^{0}	+1
Tetrachlorodibenzo-p-dioxin (TCDD)	1746-01-6	I	S	2B	$1.56\times10^{+5}$	322	$5\times10^{+7}$	+8
Tetrachloroethylene	127-18-4	I	L	3	5.1×10^{-2}	165.8	8×10^{0}	+1
Toxaphene	8001-35-2	I	S	2B	1.13	414	$5\times10^{+2}$	+3
Trichloroethylene	79-01-6	I	L/S	3/2B	1.1×10^{-2}	131.4	1×10^{0}	0
Vinyl chloride	75-01-4	S	S	1	1.75×10^{-2}(I)	62.5	1×10^{0}	0

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

Remarks:

1. Animal slopes are 95% upper-limit slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear nonthreshold model.

2. The potency index is a rounded-off slope in $(\text{mmol/kg/day})^{-1}$ and is calculated by multiplying the slopes in $(\text{mg/kg/day})^{-1}$ by the molecular weight of the compound.

3. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available.

available, data from animal oral studies and animal inhalation studies have been used in that order, since animal oral studies have been conducted for most of these compounds, and the use of such studies provides a more consistent basis for potency comparisons.

The potency index for cadmium based on the Thun et al. (1985) study of cadmium smelter workers is $6.9 \times 10^{+2}$ (mmol/kg/day)$^{-1}$. This is derived as follows: Assuming that an individual breathes 20 m^3 of air per day and weighs 70 kg, the slope estimate from the human study, 1.8×10^{-3} $(\mu g/m^3)^{-1}$, is first converted to units of $(mg/kg/day)^{-1}$ or

$$1.8 \times 10^{-3}\ (\mu g/m^3)^{-1} \times \frac{1\ \text{day}}{20\ m^3} \times \frac{1\ \mu g}{10^{-3}\ mg} \times 70\ kg = 6.1\ (mg/kg/day)^{-1}$$

Multiplying by the molecular weight of 112.4 give a potency index of $6.9 \times 10^{+2}$. Rounding off to the nearest order of magnitude gives a value of 10^{+3}, which is the scale presented on the horizontal axis of Figure 2. The index of $6.1 \times 10^{+2}$ lies in the second quartile of the 54 suspect carcinogens.

Ranking of the relative potency indices is subject to the uncertainty of comparing estimates of potency of different species using studies of different quality. Furthermore, all of the indices are based on estimates of low-dose risk using the linearized multistage extrapolation model fitted to the data at relatively high doses. Thus, relative potencies could be different at high exposures, where nonlinearities in the dose-response curve could exist.

APPENDIX A

COMPARISON OF RESULTS BY VARIOUS EXTRAPOLATION MODELS

The estimate of unit risk from animals presented in the body of this document was calculated by use of the linearized multistage model. This nonthreshold model is part of a methodology for estimating a conservative linear slope at low extrapolation doses that is usually consistent with the data at all dose levels in an experiment. The model holds that the most plausible upper limits of risk are those predicted by linear extrapolations to low levels of the dose-response relationship.

Other nonthreshold models that have been used for risk extrapolation are the one-hit, the log-probit, and the Weibull models. The one-hit model is characterized by a continuous downward curvature, but is linear at low doses. Because of its functional form, the one-hit model can be considered the linear form or first stage of the multistage model. This fact, together with the downward curvature of the one-hit model, means that the model will always yield low-level risk etimates that are at least as large as those obtained with the multistage model. In addition, whenever the data can be fitted adequately to the one-hit model, estimates based on the one-hit model and the multistage model will be comparable.

The log-probit and the Weibull models, because of their general "S" curvature, are often used for the interpretation of toxicological data in the observable range. The low-dose upward curvatures of these two models usually yield lower low-dose risk estimates than those of the one-hit or multistage models.

The log-probit model was originally used in biological assay problems such as potency assessments of toxicants and drugs, and is most often used to estimate such values as percentile lethal dose or percentile effective dose. The log-probit model was developed along stictly empirical lines, in studies where it was observed that several log dose-response relationships followed the cumulative normal probability distribution function, Φ. In fitting the log-probit model to cancer bioassay data, assuming an independent background, this relationship becomes

$$P(D;a,b,c) = c + (1-c)\ \Phi\ (a+b\log_{10} D) \quad a,b > 0 \leq c < 1$$

where P is the proportion responding at dose D, c is an estimate of the background rate, a is an estimate of the standardized mean of individual tolerances, and b is an estimate of the log-probit dose-response slope.

The one-hit model arises from the theory that a single molecule of a carcinogen has a quantifiable probability of transforming a single normal cell into a cancer cell. This model has the probability distribution function

$$P(D;a,b) = 1-\exp-(a+bd) \quad a,b > 0$$

where a and b are the parameter estimates (a = the background or zero dose rate, and b = the linear component or slope of the dose-response model). In considering the added risk over background, incorporation of Abbott's correction leads to

$$P(D;b) = 1-\exp-(bd) \quad b > 0$$

Finally, a model from the theory of carcinogenesis arises from the multihit model applied to multiple target cells. This model, known as the Weibull model, is of the form

$$P(D;b,k) = 1-\exp-(bd^k) \quad b,k > 0$$

For the power of dose only, the restriction k > 0 has been placed on this model. When k > 1, the model yields low-dose estimates of risks that are usually significantly lower than either the multistage or the one-hit models, both of which are linear at low doses. All three of these models--the multistage, the one-hit, and the Weibull--usually project risk estimates that are significantly higher at low exposure levels than those projected by the log-probit model.

The estimates of added risk for low doses for these models are given in Table A-1 for the cadmium chloride rat inhalation studies by Takenaka et al. (1983). Both maximum likelihood estimates and 95% upper confidence limits are presented. The results show that the maximum likelihood estimates of risk for the log-probit model are all less than those for the other models, and this difference increases sharply at low doses. The one-hit model yields maximum likelihood estimates slightly higher than those obtained with the multistage model, while those obtained with the Weibull model are somewhat lower.

TABLE A-1. ESTIMATES OF LOW-DOSE RISK TO HUMANS EXPOSED TO CADMIUM CHLORIDE BASED ON MALE WISTAR RATS FROM THE TAKENAKA ET AL. (1983) INHALATION STUDY DERIVED FROM FOUR DIFFERENT MODELS

	Maximum likelihood estimates of additional risks				95% upper confidence limit of additional risks			
Dose ($\mu g/m^3$)	Multistage model	One-hit model	Weibull model	Log-probit model	Multistage model[a]	One-hit model	Weibull model	Log-probit model
10^{-4}	5.5×10^{-6}	8.1×10^{-6}	1.9×10^{-7}	0	9.7×10^{-6}	1.0×10^{-5}	1.3×10^{-6}	1.2×10^{-38}
10^{-3}	5.5×10^{-5}	8.1×10^{-5}	4.1×10^{-6}	0	9.7×10^{-5}	1.0×10^{-4}	2.6×10^{-5}	8.9×10^{-25}
10^{-2}	5.5×10^{-4}	8.1×10^{-4}	8.8×10^{-5}	2.0×10^{-15}	9.7×10^{-4}	1.0×10^{-3}	3.8×10^{-4}	4.4×10^{-1}
10^{-1}	5.5×10^{-3}	8.1×10^{-3}	1.9×10^{-3}	1.3×10^{-7}	9.7×10^{-3}	1.0×10^{-2}	5.9×10^{-3}	1.5×10^{-6}
1	5.5×10^{-2}	7.8×10^{-2}	3.9×10^{-2}	7.0×10^{-3}	9.2×10^{-2}	9.5×10^{-2}	8.1×10^{-2}	2.3×10^{-2}

[a] $q_h^* = 9.7 \times 10^{-2}\ (\mu g/m^3)^{-1}$ for the multistage model; $P(d) = 1 - e^{-q_h^* d}$

APPENDIX B

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER CLASSIFICATION SYSTEM FOR THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS*

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN HUMANS

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the chemical or process.
2. Descriptive epidemiological studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agents.
3. Analytical epidemiological (case-control and cohort) studies in which individual exposure to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias which could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

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*Adapted from IARC, 1982.

The degrees of evidence for carcinogenicity from studies in humans are categorized as:

1. *Sufficient evidence* of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

. *Limited evidence* of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.

3. *Inadequate evidence*, which indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding; (c) studies were available which do not show evidence of carcinogenicity.

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN EXPERIMENTAL ANIMALS

These assessments are classified into four groups:

1. *Sufficient evidence* of carcinogenicity, which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment; (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumors in mice).

3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect; or that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since, in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

4. No data indicates that data were not available to the Working Group.

The categories sufficient evidence and limited evidence refer only to the strength of the experimental evidence that these chemicals are carcinogenic and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

EVALUATION OF CARCINOGENIC RISK TO HUMANS

At present, no objective criteria exist to interpret data from studies in experimental animals or from short-term tests directly in terms of human risk. Thus, in the absence of sufficient evidence from human studies, evaluation of the carcinogenic risk to humans was based on consideration of both the epidemiological and experimental evidence. The breadth of the categories of evidence defined above allows substantial variation within each. The decisions reached by the Working Group regarding overall risk incorporated these differences, even though they could not always be reflected adequately in the placement of an exposure into a particular category.

The chemicals, groups of chemicals, industrial processes, or occupational exposures were thus put into one of three groups:

Group 1

The chemical, group of chemicals, industrial process, or occupational exposure is carcinogenic to humans. This category was used only when there was sufficient evidence from epidemiological studies to support a causal association between the exposure and cancer.

Group 2

The chemical, group of chemicals, industrial process, or occupational exposure is probably carcinogenic to humans. This category includes exposures for which, at one extreme, the evidence of human carcinogenicity is almost "sufficient," as well as exposures for which, at the other extreme, it is inadequate. To reflect this range, the category was divided into higher (Group A) and lower (Group B) degrees of evidence. Usually, category 2A was reserved for exposures for which there was at least limited evidence of carcinogenicity to humans. The data from studies in experimental animals played an important role in assigning studies to category 2, and particularly those in Group B; thus, the combination of sufficient evidence in animals and inadequate data in humans usually resulted in a classification of 2B.

In some cases, the Working Group considered that the known chemical properties of a compound and the results from short-term tests allowed its transfer from Group 3 to 2B or from Group 2B to 2A.

Group 3

The chemical, group of chemicals, industrial process, or occupational exposure cannot be classified as to its carcinogenicity to humans.

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